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From the Children's Hospital, Linköping (Head: GILLIS HERLITZ, M. D.) and the Pediatric Department of Akademiska Sjukhuset, Uppsala
(Head: Professor BO VAHLQUIST)

Guillain-Barré's Syndrome Associated with Poliomyelitis in Newborn

by BENGT HAGBERG and GILLIS HERLITZ

Almost universally it is held nowadays that Guillain-Barré's syndrome is caused by a late neuroallergic reaction to a variety of different allergens (3, 12, 19, 36). A likely cause, such as a recent infection, vaccination, serum injection or intoxication, is present nevertheless in only about half the cases. This neural complication may follow apparently bacterial and viral diseases. It has been observed after trivial infections of the upper respiratory tract (9, 25), tonsillitis (9), lymphadenitis (9), gastroenteritis (9, 25, 28), scarlet fever (5, 7), and, perhaps most commonly, after diphtheria (9, 10, 30, 32). Among the viral diseases severe and often fatal forms of the syndrome seem to follow infectious mononucleosis (8, 16, 21, 25, 27, 38, 42). Other diseases responsible are hepatitis (11, 25, 37), measles (9), chicken pox (7, 25), and mumps (7). Typical cases have been observed after vaccinations against tetanus (11, 12, 25), diphtheria (12), smallpox (25) and rabies (33); and also after various serum injections (12). First place among toxic agents that may produce the syndrome is held by mercury which has given rise to some interesting transitions between acrodynia and polyradiculitis (3, 12, 14, 19).

Most cases of Guillain-Barré's syndrome have not unnaturally been admitted to hospital with the presumptive diagnosis of poliomyelitis — with or without a question mark. This happened in 35 of DEBRÉ's 36 cases (15). The differential diagnosis offers considerable initial difficulties but, as appears in Table 1, it is usually fairly easy after a time. When they are prevalent poliomyelitis and Guillain-Barré's syndrome may however be almost impossible to distinguish. SCHÄFER and WALTHER (39) recently discussed such combinations. At South Hannover in 1948 they observed an outbreak of poliomyelitis in which many cases displayed polyradicular symptoms. The patients exhibited a complete range of patterns from typical poliomyelitis with polyradicular symptoms, unspecific mixed forms, to cases of Guillain-Barré's syndrome so typical that the epidemiological background alone established

TABLE 1

Diagnostic symptoms and signs differentiating Guillain-Barré's syndrome from poliomyelitis.

	Guillain-Barré's syndrome	Poliomyelitis
Foregoing unspecific infection	<50 %, often weeks before	no
Specific infectious pre-stage	no	50 %, 2–5 days before neurol. symptoms
Infectious course	no	yes
Fever	no	yes
Onset of the paralyses	successive progress during days to weeks	maximum during the first few days
Type of paralyses	diffuse, symmetric, incomplete	limited, asymmetric, negligible to complete
Regress of paralyses	successive, complete	often residuals
Reflex disturbances	symmetric muscular areflexia	asymmetric disappearance corresponding to the paralyses
Meningeal signs	sometimes	always
Cerebrospinal findings (early stage)	dissociation albuminocytologique	dissociation cytoalbuminique
Prognosis	good	variable

the relation with poliomyelitis. Their investigations show that poliomyelitis is just as capable of producing Guillain-Barré's syndrome as the viral diseases mentioned. But there is a difference. Polyradicular signs may apparently develop at any time during the course of poliomyelitis; an early onset even seems to be the common thing. That is why SCHÄFER and WALTHER doubted the neuroallergic pathogenesis when the condition is associated with poliomyelitis. They were more inclined to the view that the virus was directly responsible, particularly as the symptoms appeared in epidemically clustered cases. They thought that this was the explanation of the dissimilar manifestations of various strains of poliomyelitis virus. FANCONI (15), however, denied the existence of such early forms of polyradiculitis. The albuminocytologic dissociation, which is seen often in poliomyelitis as early as the second week, might in his opinion easily provide the erroneous impression that one has to deal with a case of polyradiculitis when the C.S.F. had not been examined early in the disease.

Two case histories of Guillain-Barré's syndrome are given below. They are interesting partly because they are solitary cases during poliomyelitis outbreaks, partly because the patients were newborn. Neither of these condi-

tions show a predilection for the neonatal period. During the first weeks of life poliomyelitis is very rare indeed; and, so far as we know, Guillain-Barré's syndrome has not been described in newborns hitherto. The two youngest patients we have been able to find in the literature were 8 months old both (20, 28). DEBRÉ's series included a baby of 20 months and we have ourselves seen a classical case in a boy of 22 months (24).

Case 1. A pregnant woman was admitted at the age of 19 years to the maternity ward at Linköping Hospital on the afternoon of September 3rd, 1949, at which time the town had an outbreak of poliomyelitis. Her temperature was 38°4 C. Next morning she was delivered of a healthy boy; there were no complications. The same afternoon her legs became weak, and the following day she could not without difficulties sit up in bed unaided. On September 6th the temperature ranged between 39°8 and 40°3 C, so she was transferred to the Hospital for Intectious Diseases. Grave bilateral impairment of leg mobility was immediately discovered, and the solar and patellar reflexes were lost. The C.S.F. contained 374 cells per cmm, 333 of these were mononuclear. The readings for Nonne's and Pandy's tests were "+ +" and "+ + +", respectively. Gradually both legs, the entire right arm, the abdominal muscles, and the back, particularly on the right side, became paralytic. The patient recovered somewhat after some months, but 6 months after falling ill she still had severe paralysis of the dorsal muscles with scoliosis.

The boy weighed 3,980 g at birth and initially there were no signs of anything wrong. He was taken to the children's ward on the same day as the mother was transferred to the Hospital for Infectious Diseases (September 6th). Icterus neonatorum soon developed, but the patient was not seriously affected and appeared in all respects a healthy child. There were no neurological abnormalities and the muscular tone, mobility and reflexes were normal.

On the morning of September 14th the infant appeared limp and apathetic. The fontanelle was normal, the patellar reflexes could not be elicited and the boy was afebrile. During the course of the day the hypotonia grew worse and he did not move the extremities much. A lumbar puncture done in the afternoon revealed a straw-coloured, clear spinal fluid with respectively "+ + +" and "+ +" readings in Pandy's and Nonne's reactions and containing 56 cells per cmm, of which 36 were mononuclear. The sugar level in the C.S.F. was 68 mg% and in the blood 76 mg%. The paralysis become progressively more extensive during the next few days, and attained a maximum on September 16th when, in addition to all four extremities, the abdominal, dorsal and cervical muscles were involved. The child was atonic and hung like a rag when lifted up. Arms and legs moved not at all and the head lolled sideways without control. There was a total loss of reflexes in arms and legs. The mimic muscles functioned to some extent but he was unable to cry. He was remarkable sluggish but had a fair appetite. There was no respiratory distress, no nuchal stiffness and nothing abnormal about the fontanelle. The paralyses were strictly symmetrical from the outset. The infant was afebrile throughout and the E.S.R. never exceeded 3 mm. Arms and legs began to show a slightly better tone on September 17th and tiny spontaneous movements began to appear in hands and fingers. The continued course was characterized by a progressive and fairly rapid improvement, but the C.S.F. still showed albuminocytologic dissociation (see Table 2). After a month there was no longer any paralyses. On November 12th the infant was sent home in good condition

although the reflexes had not returned. At repeated follow-up examinations, most recently when the boy was 2 years old no sequalae could be observed. Yet it was still impossible in the lively child to produce a definite knee-jerk reflex. But none of the muscle groups of the legs were then in any way paralyzed or atrophied.

Case 2. On November 12th, 1950, a 25 years old woman in the best of health was delivered of her second child, a normal and fine boy weighing 3,100 g. The delivery was normal and there were no puerperal infections. When the infant was examined on November 18th it was doing well. Throughout the 7 days at the maternity ward the boy was in the best of health; he sucked eagerly at the breast and moved about in a completely normal manner. At the time an unusually late poliomyelitis outbreak for the season was present in Uppsala (15 cases in a month), but there were no known contacts.

On the afternoon of her homecoming — i.e. when the boy was 8 days old — the mother noted that he did not move his legs. Because the baby cried not even once, she thought he was merely being "good". But on the morrow the immobility of the legs was even more noticeable, and on the day after that he seemed feeble, sucked poorly was limp all over, and had bluish and cold extremities. He became increasingly weak during the subsequent 24 hours. On the morning of the 11th day after birth he could move only fingers and toes, and in the afternoon he developed progressive respiratory distress, general cyanosis and inability to keep the temperature constant. In the evening he was taken to the Children's Hospital at Uppsala. On arrival he was in a very poor condition and had flaccid tetraplegia, symmetrical intercostal paralysis, cold cyanosis with a temperature below 33° C, and irregular slow diaphragmatic breathing. The large fontanelle was soft, the circumference of the head 35 cm (34 at birth), the mimic muscles seemed intact, the laryngeal reflexes were absent, and the eyegrounds appeared normal. The prothrombin index was 49 and there were no visible haemorrhages. During the night, after stimulation, warming and oxygen therapy the general condition improved. Next day thoracic respiration had recommenced, and the left arm was a bit better. A lumbar puncture was done which produced a few cmm of distinctly yellow, clear fluid. It displayed a considerable albuminocytologic dissociation with 2 polynuclear and 26 mononuclear cells per cmm, and a total protein content of 240 mg%. Paper electrophoresis (Wallenius) revealed that the protein components were identically distributed, with high gammaglobulin peaks in the infant's C.S.F. and serum. Wassermann's reaction and bacterial cultures were negative. The sugar content of the C.S.F. was 68 mg% and of the blood 108 mg%. Both mother and child were negative to Bunnell's test, Sabin-Feldman's dye test and the toxoplasmosis complement fixation reaction. Faeces specimens from both mother and child were examined, with negative results, for the presence of Coxsackie and poliomyelitis virus (Gard). Unfortunately, however, the specimens did not come from the acute phase.

The condition underwent a slow improvement during the following week. The function of the respiratory muscles was partially restored. The boy was now able to get on without oxygen. He was tube fed but soon he could again suck at the breast. At the same time he began to move his left arm increasingly well and later on the right forearm and hand also moved a little. He was afebrile all the time. Two weeks after admission he freely moved the entire left arm, but the muscles of the right shoulder girdle were still completely paralyzed and the arm rotated inwards in a fixed position. As before the lower extremities were paralyzed. The upper and middle abdominal reflexes, as well as the brachioradial and tricipital, had turned weakly positive. During the course of the third week the C.S.F. became fully normal (see Table 2), but apart from this

TABLE 2

Cells and protein content of the cerebrospinal fluid in the two patients.

	Day in disease	Cells $\frac{\text{polyn.}}{\text{monon.}}$ / cmm	Pandy	Nonne	Total proteins mg %
Pat. no. 1	1	20/36	+ + +	+ +	
	8	28/20	+ +	(+)	164
	13	5	+ +	+	180
	22	3	+	(+)	–
	41	2	+ +	(+)	80
Pat. no. 2	4	2/26	+ + + +	+ + +	240
	10	1/11	+ + +	+ +	220
	21	1/6	+	–	52
	58	0/1	–	–	32

the clinical picture became stationary the time being. He was subjected to repeated follow-up examinations for recurrent respiratory tract infections with respiratory distress. Last time at the age of eight months he was treated at the Children's Clinic for some weeks. Then his mental development showed a fairly satisfactory progress, but his motor functions remained badly impaired. He had learnt to lift his right arm to his mouth with the aid of the left. Both legs were still completely paralyzed. Moreover there was a symmetrical atrophy of the extremities and, particularly, of the intercostal muscles. At the last examination no deep reflexes could be produced.

Discussion. In the first case the mother undoubtedly had typical poliomyelitis. The child on the other hand had typical Guillain-Barré's syndrome with symmetrical, flaccid tetraplegia, afebrility, marked albuminocytologic dissociation, and complete remission of the extensive paralyses. That the child's disease was associated with the mother's was a reasonable assumption in this case. In newborns cerebral lesions following parturition may show extremely varied manifestations, but not the picture presented here with extensive flaccid paralyses which healed so completely without spasticity. Diseases of the nervous system other than those mentioned here need scarcely be considered. The problem is simply in what manner poliomyelitis virus gave rise to a polyradicular reaction in the child. Was it merely an unspecific neuroallergic response to the maternal infection, or did the boy actually have atypical poliomyelitis? Initially presenting an almost identical clinical picture the second case hardly left room for doubt on this point. Here the continued course resulted in partial restitution only. Distributed asymmetrically and associated with typical atrophies, the persistent paralyses were characteristic of poliomyelitis. The absence of spasticity and the so far

TABLE 3

Cases of poliomyelitis in children less than two weeks old.

No.	Author	Age at onset, days	History and symptomatology	Virus inoculation	LP Day in disease	C. S. F. Findings	
						Total proteins	Cells $\frac{\text{polyn.}}{\text{monon.}}$ / cmm
1	FRØVIG 1947	4	Mother: incipient polio at delivery. Child: fever 4th day; tetraplegia and general flaccidity 8th day; residual state of asymmetric paralyses; lumbar puncture not done.	not done			
2	BASKINS & cow. 1950	5	Mother: incipient polio at delivery. Child: fever 5th day; extreme general flaccidity; death in respiratory paralysis; necropsy: polio.	?	1	300 mg %	11/97
3	SHELOKOV & WEINSTEIN 1951	6	Mother: at delivery in respirator, dying in polio. Child: 6th day watery stools, lassitude and lethargy. Strikingly limp. Meningeal signs. Asymmetric paralyses in the legs. Partial improvement only.	not done	2	224 mg %	22/165
4	SEVERIN 1939	7	Mother: cystitis. Child: vesical paralysis 7th day; flaccid tetraplegia (right more than left) 10th day; afebrile; death 11th day; necropsy: polio.	+	3	Pandy + Nonne +	5/191
5	KRARUP & PLUM 1947	8	Sucked breast poorly; completely limp 13th day; total tetraplegia; death 17th day; necropsy: polio.	not done	5	not raised	0/51
6	BASKINS & cow. 1950	8	Mother: polio at delivery. Child: fever 8th day; flaccid tetraplegia & respiratory paralysis & death 11th day; necropsy: polio.	+	3	120 mg %	12/32

TABLE 3 (counts.)

TABLE 3 (counts.)

No.	Author	Age at onset, days	History and symptomatology	Virus inoculation	LP Day in disease	C. S. F. Findings	
						Total proteins	Cells polyn./monon./cmm
7	HAGBERG & HERLITZ 1952 (case 2)	8	Mother: healthy. Child: progressive flaccid tetraplegia for 3 days; residual state with considerable polio-like paralysis.	(−)	4	240 mg %	2/26
8	MOUTON & cow. 1950	10	Mother: healthy. Child: fever 10th day; limp; right arm paralytic; in time tetraplegia; residual paralyses.	not done	4	Pandy + +	0/37
9	HAGBERG & HERLITZ 1952 (case 1)	10	Mother: polio at delivery. Child: flaccid tetraplegia & general limpness 10th day, exacerbating over 48 hours; afebrile; complete recovery.	not done	1	Pandy + + + Nonne + +	20/36
					8	164 mg %	28/20
10	BIERMANN & PISZCEK 1944	11	Mother: died in polio. Child: fever 11th day; flaccid tetraplegia 14th day; residual paralysis right leg.	not done	2	not done	12/45
11	GUNEWARDENE 1918	12	Mother: healthy. Child: initial flaccid tetraplegia & paralyses of neck & abdomen; slight residual paralysis.	not done	7	"raised"	9/91
					15	"raised"	1/40
12	PALMSTIERNA 1945	12	Mother: polio, caesarean delivery at moment of death; Child: right leg paralyzed 12th day; all limbs limp later; residual paralysis in both legs.	not done	1	Pandy + + +	70
13	PALMSTIERNA 1945	12	Mother: puerperal polio. Child: fever but no paralysis 12th day; reflexes normal; complete recovery.	not done	1	Pandy + + Nonne + +	202

normal mental development in paralysis of such severity as in the second case make it unlikely that an intracranial haemorrhage was responsible. Accordingly the ultimate diagnosis was Guillain-Barré's syndrome following poliomyelitis during the first week of life.

The similar and atypical manifestations at the onset in both these cases raised the question of the symptoms and signs of poliomyelitis in newborns. Probably no more than about 25 cases have been published at present, and several of them are described at second hand, often many years after the disease occurred (1, 2, 47). Directly observed and, well documented cases in subjects under two weeks of age (1, 4, 18, 23, 29, 34, 35, 40, 41) have been assembled in Table 3. Despite the extremely varied outcome from case to case one is struck by the almost consistently occurring flaccidity and tetraplegia when the disease culminated. Our patients in other words seem to have followed the rule rather than being clinical curiosities in their class. Afebrility may be added to the polyradicular manifestations in 5 of the 13 children. Albuminocytologic dissociation seems likewise to be commoner in this than in other age classes, even though it seldom is more than relative. Remarkably early and very high total protein levels were nevertheless noted in all the 5 cases in which a quantitative estimation was done. Only 2 of the 13 cases showed no signs of having an increased protein content. If this is compared with C.S.F. studies on poliomyelitic children of all ages, it will be found that only a few values are remarkably high, and then as a rule only when the disease has been present for two weeks or more (17). The cases observed by us are the only ones exhibiting polyradicular manifestations during separate outbreaks. Consequently one cannot in our cases speak of a *genius epidemicus* which, according to SCHÄFER and WALTHER, might be responsible for an accumulation of cases. The only thing that distinguishes these children from patients of other ages is that they were united with the mothers during all or part of the incubation period. It is not unlikely that therein might lie the reason for the deviating clinical manifestations. If so, the debated question of intrauterine infection or not assumes a high degree of importance.

In the current literature many cases are reported of poliomyelitis in pregnant women close to the time of delivery. Practically all of them have given birth to perfectly normal infants why transplacental infection with poliomyelitis virus is doubted (22) or at least appears to be extremely unusual (6). Contamination with the mother's intestinal contents at delivery has been thought to be an adequate explanation for poliomyelitis in the newborn period. But in a case reported by PALMSTIERNA (35), where the mother was delivered by Caesarean section as she was dying, transplacental transmission seemed to be the most probable explanation to the baby's infection on the 12th day of life. AYCOCK's (40) and FRØVIG's (18) reports of an onset as early

as the 2nd and 4th days of life, respectively, point in a similar direction, for it is believed that the shortest incubation period is 5 days (1). If the latter statement is correct, the clinching proof of intrauterine transmission is provided by BASKINS & coworkers' (1) report of a case in which death occurred on the 7th day of life and histological changes were found indicating that virus had been active in the nervous system for at least 4 days. If intrauterine infection were impossible, the incubation period could not have exceeded 84 hours. Merely the fact that poliomyelitis virus so far has not been demonstrated in the bloodstream of persons with poliomyelitis contravenes a transplacental transmission[1]. In other words the majority of observations bear out the existence of an intrauterine route of infection.

It consequently seems to us that the polyradicular manifestations in poliomyelitis in newborns might be explained as follows; the poliovirus of the mother is transmitted during intrauterine life at the same time as the foetus passively participates in the mother's incipient immunological adaptation. The child will later respond to the infection itself partly with poliomyelitic changes of standard type and partly with polyradicular manifestations due to an early neuroallergic adaptation. A similar diaplacental transmission of toxins with similar effects would be conceivable too, but only in cases when the child's paralyses show complete remission (as in our case 1). Both these explanations, however, demand that the mother had poliomyelitis at the time of delivery, either in clinically manifest or subclinical form. Another possibility may be that newborns show a specific type of response to infection with poliomyelitis — infants often react to infections in a deviating manner. At present, however, there is no definite evidence in particular favour of any of these theories, but the fact nevertheless remains that newborns with poliomyelitis show a high incidence of polyradicular signs.

Summary

Two cases of Guillain-Barré's syndrome in newborns with probable poliomyelitis are reported. The infants were 10 and 8 days old. Both were afebrile, had general flaccidity with tetraplegia and initially the cerebrospinal fluid showed marked albuminocytologic dissociation. The mother of the first had typical poliomyelitis, starting on the day of delivery. This boy recovered completely. The other developed residual paralysis characteristic of poliomyelitis. A survey of the well documented cases of poliomyelitis in infants under two weeks of age reveals that general flaccidity and elevated cerebrospinal protein levels seem to be the rule rather than an exception. Different possibilities for this phenomenon are discussed.

[1] Since this paper was submitted for publication HORSTMANN (Proceed. of the Soc. for Exper. Biology *73*: 417, 1952) demonstrated, however, that poliomyelitis virus was to be found in the blood of orally infected monkeys during the incubation period.

Syndrome de Guillain-Barré associé à une poliomyélite chez les nouveaux-nés.

Deux cas de syndrome de Guillain-Barré chez des nouveaux-nés avec poliomyélite probable sont rapportés. Les enfants avaient 8 et 10 jours. Tous les deux étaient afébrile, avaient une flaccidité générale avec quadriplégie et initialement le liquide céphalo-rachidien avait montré une dissociation albumino-cytologique marquée. La mère du premier avait une poliomyélite typique, débutant le jour de l'accouchement. Cet enfant récupéra complétement. L'autre évolua vers une paralysie résiduelle caractéristique de la poliomyélite. Une revue générale de cas trés documentés de poliomyélite chez des enfants agés de moins de 2 semaines montrait que la flaccidité générale et que l'augmentation destaux de protéines cérébrospinales étaient la régle plutot que l'exception. On discute en outre des différentes origines de ce phénoménes.

Guillain-Barré-Syndrom mit Poliomyelitis bei Neugeborenen.

Bericht über 2 Fälle von Guillain-Berré-Syndrom bei Neugeborenen, die wahrscheinlich eine Poliomyelitis hatten. Die Säuglinge waren 8 und 10 Tage alt. Beide zeigten kein Fieber, allgemeine Schlaffheit mit Tetraplegie und der Liquor cerebrospinalis wies anfänglich eine deutliche Zell-Eiweissdissoziation auf. Die Mutter des ersten Kindes hatte eine typische, am Tage der Entbindung beginnende, Poliomyelitis. Dieser Junge erholte sich vollständig. Beim anderen blieben für Poliomyelitis typische Paralysen zurück. Ein Überblick über die gut unterbauten Fälle von Poliomyelitis bei Kindern, die weniger als 2 Wochen alt sind, ergibt, dass allgemeine Schlaffheit und erhöhter Liquoreiweisspiegel eher die Regel als die Ausnahme zu sein scheint. Verschiedene, für dieses Phänomen verantwortliche Möglichkeiten werden diskutiert.

Sindrome de Guillain-Barré asociado a poliomielitis en recien nacidos.

Se comunican dos casos de sindrome de Guillain-Barré en recien nacidos asociados a una probable poliomielitis. Estos niños tenian 8 y 10 dias de edad respectivamente, Ambos casos eran afebriles, presentaban flacidez generalizada con tetraplejia e inicialmente en el liquido cefalo-raquideo se observaba una marcada disociacion albumino-citologica. La madre del primer niño tenia una poliomielitis tipica iniciada el dia del parto. Este niño se recupero completamente. El otro caso desarrollo una paralisis residual caracteristica de poliomielitis. Una revision sobre los bien conocidos casos de poliomielitis en niños por debajo de las dos semanas de edad revela que la flacidez general y una elevada cifra de proteinas en el liquido cefaloraquideo suelen ser la regla general en vez de una excepcion. Se discuten las diversas maneras como puede interpretarse este fenomeno.

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Akademiska sjukhuset
Uppsala. Sweden.

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On Psychogenic Obesity in Children. III

by FLEMMING QUAADE

The present article is part of an inquiry, not yet concluded, into the conditions, social, anthropological, and endocrinological, of adipose children. The final results of this inquiry will be published subsequently.

For my material I have examined the total population of four Copenhagen County Council Schools, i.e. 3771 children aged between six and sixteen. Among the 3771 children information was sought about 2273 children. The dispersion of this group as regards state of nutrition did not differ from that of the total population. The schools are selected so as to be reasonably representative of all social strata in Copenhagen. Let it be said at once, however, that a material of school-children falls short of the ideal in three respects: 1) it does not comprise children under six, 2) it excludes from the start the considerably defective as to intelligence, 3) its adipose fraction does not contain so many extremely fat children as can be found in a clinical material. But apart from this there can be no risk of any undesirable selection, seeing that schooling is compulsory for all children, and they will consequently be put down on the cardindexes of the schools.

Of the 2273 children mentioned 137 (6.0 per cent) were adipose, — and I use this term for any child whose weight exceeded the mean value for a height group by more than twice the standard deviation. The investigation of the individual surroundings, the results of which will be given below, were made on 36 adipose children (18 boys and 18 girls). These 36 children were selected as representative of the total group of adipose children, as regards sex, age, degree of overweight, position in family, economic situation, and parents' state of nutrition. Information was obtained from repeated interviews with parents and child, and often supplemented with the opinion of the school; the method was closely patterned on that used by BRUCH (1940 b). I want to emphasize that in no case was I refused admittance to the homes, nor did the parents ever decline to give me the information I wanted. It is true that a few parents seemed indifferent or even disobliging at first, but in every single case I managed to rouse their interest, and they promised to continue contact. This favourable circumstance is worthy of note, for it meant that I never had to substitute any of the already selected patients in order to find parents that were willing to cooperate, — a measure which would undoubtedly have been most undesirable for an investigation, the pur-

pose of which among other things was to affirm or invalidate a supposition about the etiological importance of overprotection and excessive care. In this connection I want to call attention to the fact that the attitude of the parents of BRUCH's 160 adipose children was such as to make it necessary for her to make a choice among parents willing to cooperate in order to find the 40 families whose family frame she investigated, and who admittedly made up a representative part of the total material as regards race, degree of overweight, and position in family: "These particular families were selected on the basis of willingness and ability to cooperate in giving the information, though a number of them were uncooperative in the clinical treatment of their children."

I timed my home visits in such a way as to make it possible for me in practically all cases to talk to the mother or the father in private; in the majority of cases I also found an opportunity to observe the parents together. In all homes I had occasion to note the mother's attitude in her contact with the child and its possible brothers and sisters, and I very often contrived to watch personally the relations between father and child. The interviews, which were often of considerable length, were continued and resumed until I had a feeling of having 'exhausted' the case, or — where certain problems were not yet clarified — till I felt convinced that I could not get much further with ordinary confidential talks, and that possible additional information could only be reached by employing a technique of deep-probing psychology. I never wrote down anything during the interviews, but I always put my impressions on paper immediately after the visits. I always procured general information about both parents as to age, occupation, diseases, also their childhood and youth, frequency of obesity in the family, duration and condition of their married life, food intake of the family, the question of the treatment of the child, etc. As to the mother I concentrated my attention specially on her pregnancy, her reaction at that time, her information about the child's antecedents, development, psyche, habits, independence, and behaviour generally. Besides I took careful note of every peculiarity of phrase, tone, or expression that might betray her attitude to her husband, the child, and its possible brothers or sisters. More than anything I dwelt on the possibility of psychogenic alterations in appetite and state of nutrition; and in cases where the child had not 'always' been adipose I gathered — so far as it was feasible — information about the exact time for the onset of obesity. On this point it was a great help that I had ample opportunity to study photos of the child, taken in different periods of its life.

As to the food intake of the adipose children I can briefly state as my conviction that without exception they were great eaters. As to the quality of the food it was my impression that starch played a prominent part in the diet, and that the patients particularly eat great quantities of potatoes, bread, cereal, and the typical Danish 'baked sauce' (i.e. gravy cooked with butter and flour). It was common to find parents and children unwilling or hesitating before they would admit that their food intake was great. But in nearly all such cases they changed their opinions when I became on more confidential terms with the families. In some cases the parents betrayed the correct state of affairs without wanting to, and in spite of the fact that they went on denying that the child eat much. As the general clinical examination in no case revealed any diseases — particularly endocrine ones — which might be considered causative of the abnormal state of nutrition, I fully agree with BRUCH when she asserts that the sheer physiological origin of adiposity can be quite naturally explained by means of simple energetic considerations. Our next question, then, will be: does the continued existence of obesity necessitate a great food intake? And here we are faced

with a problem of the greatest importance, practical and theoretical: should adiposity be regarded simply as sequelae after a period of excessive eating? Or does it demand a continued active maintenance through a supply of food which is greater than the number of calories that the same person would have to receive in order to be in a normal state of nutrition? It is true that BRUCH is convinced that an excessive food intake always takes place in the developing phase of adiposity where the weight increase exceeds the values that follow from the child's normal development. But she does not think that the food intake *need* be very great in the period where the obese child's weight is increasing at a normal rate. In contradistinction to this I must say with conviction that for its continued existence adiposity will always demand maintenance through a supply of food that clearly exceeds the quantities necessary for the balance of energy in the same person, normally or insufficiently nourished. This conviction of mine is not supported by figures, seeing that I have not been able to find a reliable exponent for the children's consumption of calories, but it is based on the observation that all 36 obese children eat much in periods where their state of nutrition was nearly unaltered, though the amount of food which they had at the time when they started to grow fat was even greater. And my impression is further confirmed by the literature on the subject, which tells us that the basal metabolism of obese children distinctly exceeds the values applying to children of the same age and height, but of normal weight (TALBOT, WILSON and WORCESTER 1937, BRUCH 1939 & 1940 a, MOSSBERG 1948).

In the homes I often noticed that at first the parents disagreed with my opinion concerning the appearance of the child. Apart from two cases, however, they all agreed in the end and confessed that the child was overweight. But rarely did they look upon the obesity as a pathological phenomenon, they preferred to regard it as a variation within the normal and of no great importance, a state of things that did not call for active measures. Only a few thought that endocrine disturbances were behind the obesity. It was significant that the word 'fat' was used by only one mother; 'plump' was somewhat more frequent; but mostly the children were just 'vigorous' or perhaps 'stout.' On several occasions I came across the idea that children of elephantine appearance and a solid density of subcutis were not adipose at all: the increase of bulk was due to muscles so the darlings were ever so 'strong.' Sometimes, however, the vote was unanimous, the tissue deposits did consist of fat, — but then there were positive pendulous skin formations on the trunk.

Lack of space prevents an individual and detailed documentation of what I found in the surroundings of the 36 children; the following paragraphs will only give a brief summary of my observations.

I have already mentioned that the 36 children examined were selected as representative of the total material comprising 137 adipose children, also as regards the income of the bread-winner. Naturally most of the homes were modest ones, but nevertheless it is very difficult to point out any uniformity in the social conditions under which the children lived. Particularly it is worth noting that the homes hardly ever had that exaggerated imitating-their-betters neatness which was so characteristic of the homes visited by BRUCH. Only once was it clear that the parents' idea of comfort, orderliness, and nice furniture could be a serious hindrance for the normal expansion of the child at home. Otherwise it was the rule that children from all income classes were allowed, within reasonable limits, to use the rooms.

The Fathers of the Adipose Children

Although many fathers were of humble stock and had met the hardships of life early, by far the most (31) gave vent either to great satisfaction with their childhood, or they called it 'quiet and ordinary.' Only in five instances had the father grown up in an atmosphere of insufficient understanding or open conflict. Three of these men had become apparently good husbands and fathers, who were content with the life they had created for themselves in spite of a handicap in the start. But in the two other cases it was my impression that the child was exposed to paternal 'rejection,' though I found no convincing reason to suppose that this fact was of etiological importance for the obesity of the child. Fathers were rare who thought they had fallen short of their vocation and were discontented with their position in life, and deserved the BRUCHIAN label: 'lacking in initiative, drive, and ambition.' It is true that one father confessed himself unfit for a responsible and superior job, but his wife admired and respected him, and a stable, patriarchal atmosphere reigned in the house. Only two cases suggested the husband as henpecked.

The Mothers of the Adipose Children

Also on this subject it is difficult to make generalisations. Three women told me that their childhood had been unhappy. This number is a small one if we remember BRUCH's observations which prove that she had no need to pump the mothers who gushed their bitter and self-pitying comments on a joyless and insecure childhood. Of the three mothers in my material one was clearly neurotic, and I could safely ascribe her symptoms to unhappy and ghastly reminiscences. But she was far from self-pity, and besides I thought it right to conclude that the child's adiposity was without etiological connection with the mother's 'nerves,' — there was a tradition in that home of good and abundant food, the son had been adipose ever since he was a baby, and the mother's reaction on her pregnancy as well as her subsequent attitude to the boy and his problems displayed nothing that was abnormal. The second of the three mothers mentioned was very fond of children; her sad reminiscences had worked constructively, and she had created a peaceful and harmonious home. The third mother, however, displayed nearly all the features that in BRUCH's observations are described as characteristic; and it was clear that the memory of an unsafe childhood spent in poverty was instrumental in making her overfeed her family. But if there was any ambivalence at all in her relation to the child, it was at least very weak. For the rest, suffice it to say that the great majority of mothers in my material were honest Copen-

hagen matrons and ordinary housewives, who were reasonably satisfied with life and loved husband and children. Lamentations over hopes that failed and wishes unredeemed were few and far between.

Relation between Parents of Adipose Children

All that has been said up till now tends to the conclusion that the great majority of married lives in my material seemed 'normal,' and that the relations between husband and wife but rarely displayed anomalies discernible by the applied method of investigation. Of course the parents often told me that opinions might differ and occasionally they would even quarrel, but as a rule the children were not involved, and soon the atmosphere had cleared.

Only four cases deserve further mention on account of discord between the parents of the adipose child. In one of these cases the child had witnessed — perhaps joined — dramatic quarrels between the parents. The mother died after having been bedridden for long periods; from what I was told the child had not taken much to her, but had at an early stage transferred her love to her later stepmother. The patient was not overprotected, but I think she was subject to rejection. She belongs to the group about which I have considered it possible to suppose that obesity was started and maintained by patho-psychological mechanisms. The second case deals with a much neglected divorce child, whose whole imagination was dominated by most unusual oscillations of feeling between the parents. The obesity of this child is presumably due to psychogenic disturbances in the regulation of appetite. But the case was not really like the typical BRUCH constellation, and in my opinion should rather be classed among the adiposity cases produced by acute psychical insults. Case III: the parents did not wash their dirty linen in public, and they were loyal when talking about each other, but it was obvious that they had not much in common. Neither did the child meet sufficient understanding and interest from them, and particularly in its early years must have felt rejected. However, there was no chronological connection whatsoever between alterations in appetite, state of nutrition and relations to parents. In case IV the atmosphere at home was bad, the father was hard and brusque, and the mother was not able to counterbalance his influence. There was no overprotection, on the contrary, the children were scared and cowed, and they tried to stick together and included their mother in their common front against the father. This alone will be enough to show that the family differed from the typical BRUCH cases in essential ways; and I found that non-pathological causes were sufficient to explain the obesity of the child.

Father v. adipose child

I detected the presence of paternal overprotection in one case. The father was obviously of a somewhat frigid disposition, but the child seemed to be his whole world, and I consider it to be out of the question that food should have been used as emotional substitute. Obesity seemed to be the result of well-intentioned — though mistaken — attempts in dietary hygienics. Another case showed signs of overprotection from both parents, but these symp-

toms did not appear until the child had been violated, and are naturally explained by the parents' fear of a repeated attack. (Incidentally, the crime did not coincide with the beginning or progression of obesity, on the contrary, she lost weight after the incident.) However exaggerated and wrong this protection may be, it has evidently nothing in common with the BRUCHIAN overprotection, which is the outward manifestation of insufficient love.

Two cases of paternal rejection have already been mentioned in the latter part of the previous chapter. One case remains: here the father was too critical and demanding in his attitude to the child, and it struck me that this might be a contributary cause in a psychogenic release of obesity, also because this child felt strongly attached to her father, and was deeply hurt by his criticism. The child's schoolwork was the main target for the father's critical remarks, and the obesity developed badly exactly when the child started school.

In all other cases I found the father and his adipose child to be on natural terms, and in quite a number of cases the relationship between the two was excellent, bearing the stamp of great confidence and good comradeship.

Mother v. adipose child

Great weights at birth occurred rather frequently in my material, and in a little more than half the cases (at least 19) there could hardly be any doubt but that obesity had existed from birth or at any rate from a tender age where the child's conscious life can scarcely have been very differentiated. We remember the way in which BRUCH explains the adiposity of such children: on their very entrance into this world they meet an ambivalent and overfeeding mother, whose attitude to her potentially fat offspring is greatly decided by her dislike for pregnancy, dissatisfaction with the child's sex, or other un-motherly feelings.

In five cases from my material I was told, or it was implied, that the later adipose child had not been wanted. Two of these women were rather sluggish, of the kind that rarely have more than one child. One of them gave no explicit reason for her lack of interest in children, the other declared frankly that at first she did not like children at all. In this latter case at any rate I fell certain that the mother's attitude had no etiological relevance to the child's obesity; the patient's overweight was evident from birth, and already in the maternal home he created a sensation on account of his insatiable appetite; doctors and nurses often stopped and laughed when he was suckled — 'just like a little bull.' As I said before, the mother was somewhat sluggish and frigid, but she was not hostile or testy towards the child, and he and the father got on exceedingly well. In a third case the child had been conceived under circumstances that were socially compromising to the mother. Maternal

rejection combined with an altogether strong tension between the members of the family must have contributed definitely to adiposity in this child, who had an outspoken tendency to console herself with exaggerated eating. Case IV was also one in which adiposity might be ascribed to 'eating-consolation,' but the mother's original attitude to her pregnancy was scarcely of any importance, the child had started growing fat when the family moved to Copenhagen; he could not adjust himself to the new surrounding, made no friends, and besides he unfortunately damaged his knee, which necessitated protracted immobility. In the fifth case, where the child was not wanted, the mother had nearly all the peculiarities advanced by BRUCH; she was overprotective, anxious about the child's bodily and moral safety, overfeeding, — and the disappointment with the sex of the child had not yet worn off.

In four cases it was clear that the sex of the patient had been disappointing to the mother, but in only one of these cases — the only typical BRUCH-case in my material — I thought it safe to presume that this fact had contributed to developing obesity in the child. Apart from this exception, the mother's wish as to sex had changed quite naturally after she had given birth to the child, and she loved the baby for what it was.

Varying degrees of maternal overprotection was present in four cases. One of them had been mentioned already, but let it be remembered that protective measures were not taken until the child had been raped. In the second case overprotection was definitely a fact, but I could detect no hostile elements in the mother's attitude. The child became adipose when eight years of age; it had then for the first time been allowed to spend the summer holidays away from home, so incidentally it was not the high tide of motherly solicitude, but its temporary absence that made the child seek consolation in food. A third case showed uncertain signs of maternal overprotection minus hostility. Far more convincing was the overprotection in the fourth case, the 'typical BRUCH case' just mentioned.

Certain signs of maternal rejection were stated in eight cases. In four cases out of these the mother would get into a temper on the occasions when she and the child fell out, and sometimes she sounded slightly annoyed when talking about the child. In the remaining four cases the mother did not seem to me to be what I would call hostile, she was rather without ardour or at least without interest in her association with the child. It is remarkable that the typical ambivalence so much emphasized by BRUCH, namely overprotection cum overfeeding combined with rejection, could be ascertained in only one case in my material, and even then the hostile elements were but faint, in fact they were only discernible because the mother did not want to have more children, and because she would have preferred the fat boy to be a girl, — and then there was the hostility that one can imagine looming up

behind an exaggerated fear that something should happen to the child when out on its own. I have now mentioned a number of cases where maternal rejection could be stated with more or less certainty, and there were always positive emotional ingredients in the mothers' attitude to their children. So of course we could say that these women were ambivalent, but their rejection was not mingled with overprotection and overfeeding, on the contrary they displayed much more valuable characteristics in greater harmony with true motherly love.

Nor was the anxiety for the welfare of the children, which BRUCH has dwelt on so often, really significant for the mothers in my material. Some such feelings could be traced in five mothers. In my typical BRUCH case the fear was unmistakable, but she could give no reason. Three mothers were anxious about the morals of the children, their choice of playmates, or participation in sexual games. The fear was strongly pronounced only in the fifth case, and here we find a sensible reason — and that was the only reason too — in the fact that the child had been a victim of outrageous assault.

My general impression is that though many mothers could very well be said to overfeed their children, it appeared to me to be a strained interpretation to try to explain the fact along the lines laid out by BRUCH, as I shall presently point out. For I was more and more convinced that the attitude of the mothers — and for that matter of the fathers — to food and food intake was not a cloak that covered insufficient love; the roots went to other strata of the soul, less easily definable perhaps, but also far less pathological.

Personality of Adipose Children

I could prove in nearly all the children in my material that the abnormal state of nutrition had caused psychical difficulties. These troubles, which must be ranked as secondary to the adiposity, were, however, far from being equally pronounced in all cases. It was obvious that numerous smaller children suffered much at being the target of their playmates' jokes. In bigger children the wish of slimming was rather based on cosmetic reasons. Other cases — in my material at least five — seemed but little inconvenienced. It was my impression that the weight with which these secondary difficulties told on the separate cases, did not depend on the degree of obesity and the age of the child to any great extent; much more important were less conspicuous factors, among which I find it natural to give particular prominence to the child's 'constitutional' psychical robustness, mental assertiveness and expansive force. Consequently I had great difficulty in finding other characteristics which can justly be regarded as joint psychical possession of adipose children. The 'immaturity, overdependence, and lack of aggressiveness' so

often referred to by BRUCH were far from being present in all the cases examined by me. Only three children seemed to be somewhat more immature than should be considered normal for their age. As to one overprotected child I discovered that it was an active process chiefly on the mother's side, and that the child was not really dependent. And I found several cases where the children for all their obesity and difficulties were nothing if not independent. As it is natural to expect, the remainder of my material comprises cases where the children owing to the secondary difficulties had lost a considerable part of their self-confidence and their keenness in joining 'the others' in their games. But many of them had been boisterous and active youngsters before putting on fat, and on the whole I could not lay my finger on any fundamental traits dominating the personality of the children in my material, none that I could honestly say should have made them specially talented for an adiposity-provoking, psycho-pathological interplay with their mothers.

It must be added that in some cases bodily activity was so reduced as to justify the supposition that a decreased loss of calories might contribute to originating obesity. In other cases only the excessive food intake could explain why the children had not long ago 'run out of fatness'; one boy often ran up the stairs to the fifth floor to get food or information about the menu, and several girls, too, were on the move all day, though for other and commoner reasons.

No signs of a uniform reacting ability in the children's appetite could be proved; some (five children) were said definitely to eat for consolation, but just as many lost their appetite when feeling low (three) or having been subject to a heavy psychical strain (two). And I also met several children, whose obesity began when they were babies, and who had later been through an unmistakable period of self-assertive obstinacy.

Summing up I am bound to say that my observations of the personality of these 36 children did not tempt me to generalisation. The material appeared to me too inhomogenous, and my patients seemed to be as different from one another as any 36 children supposedly would have been if they had been furnished with ample panniculus and a corresponding opportunity to react to the concomitant difficulties.

In an investigation of 36 obese children, their parents, brothers, and sisters, it was to be expected a priori that occasional conformity would be found as to some of the numerous points that BRUCH puts down as being relevant. Such sporadic occurrence of features which we find described in the characteristic BRUCH constellations does not justify in itself the supposition of a psychogenic etiology to the obesity of the child in question. In my material the features were so inconstant that I must consider them merely accidental. The simple statement of a simultaneous existence of adiposity and perhaps

one or two of the alleged characteristics, does not allow me to use psychogenic causes to explain the obesity in these cases. Wherever possible I have tried to confirm or refute the aetiological relationship between obesity and the BRUCH-elements, or between obesity and other demonstrable phenomena. My judgment of the cases, therefore, is based principally on three points:

1) the general impression of the present and earlier emotional status of the child and its surroundings.

2) the demonstration or exclusion of 'eating-consolation.' I use this term comprehensively for all cases in which I consider that the child under lighter or heavier emotional strain is inclined to eat more than usual.

3) simple chronological reasonings for all the cases where specifications as to the onset or possible exacerbation of obesity were sufficiently exact and reliable (weight diagrams, photos, convincing testimony from the next of kin) so as to allow the demonstrable phenomena to be correlated in time with alterations in the child's state of nutrition. In the numerous cases (at least 19) where adiposity was stated to have lasted from the first year, and where the state of nutrition had not changed to any great extent since, I concentrated my attention on possible traits in the parents, particularly the mothers, which might be supposed to have caused a psycho-pathological or at any rate undesirable change in their attitude to the child already in its babyhood. Where such traits could not be proved, the cases are most frequently regarded as simple 'eating-habit adiposity.'

I naturally had to consider the timeliness of a control group of 'normal' children. Individual inquiries like these into the surroundings of children take much time, so it was impossible to use the whole non-obese population schoolchildren as a comparative list. I found it more sensible first to select and examine an adiposity group of a size similar to that of BRUCH (1940 b) and to compare my material with hers in order to ascertain if the characteristics pointed out by her were recognizable in mine. In case of apparent conformity — or if other psychological configurations in my material should be demonstrable with sufficient frequency as to be considered characteristic for adipose children — then it would be necessary to compare the frequency of the said traits with a material of non-obese children, always remembering the overwhelming difficulty in making a reliable selection of such a control group. As — after a careful inquiry into the conditions of 36 obese children — it appeared that no such characteristics could be found in my material as those described by BRUCH with anything like the frequency laid down by her; and as moreover my investigation did not tend to prove other elements as being conspicuous in obese children, the question of an individually examined control group vanished. Actually BRUCH's investigation and mine only agreed to a certain extent as to the difficulties caused by obesity. But although they

Incident of alleged relevance	BRUCH (out of 40)	Present series (out of 36)
Father's unhappy childhood	most	5
Mother's » »	most	3
Father weak, unaggressive	most	1
Father hen-pecked	many	2
Proved matrimonial discord	at least 21	4
Child welcome	2	most
Child not wanted	at least 15	5
Disappointment at sex of child	at least 11	4
Rejection only	not many	8
Rejection plus overprotection	nearly all	1
Fear for moral and physical safety	nearly all	5
Dependence in child	most	3
Pronounced independence in child	hardly any	4
Eating-consolation	perhaps all	5
Loss of appetite through 'low spirits' or psychical insult	hardly any	5
Acute psychical handicap as probable cause of obesity	4?	3 (4?)
Outspoken secondary difficulties	all	nearly all

might be extremely prominent in the individual patient, they rarely allowed me to jump to the conclusion that fundamental, psychical qualities had made this particular child adipose. It was seldom that the reactions to secondary difficulties could be relied upon as being important in the maintenance of obesity. These secondary difficulties — the only frequent occurrences in my material — were most certainly of absorbing human and medical interest, but all the same they were of no fundamental relevance to the student whose main purpose was to investigate the etiology of obesity.

The table above will show how great is the difference between BRUCH's material and my own, regarding the traits which she has claimed as characteristic or even indispensable components in her theory of adiposity.

What can be the reason of the great difference between BRUCH's results and mine? I cannot help thinking that the risk of error must have been great in an adiposity material like the one made up by BRUCH. For one thing, so many disappointed, petulant mothers and submissive fathers, so many childhoods miserable in retrospection, such failures in married life, such an amount of women disgusted with their pregnancy — horrors like these seem to be characteristic of a population like the one from which BRUCH took her material: the lowest layers of New York, a city more famous for size than for softness. But in no way need such horrors be characteristic of the parents of adipose children generally. I quickly realized that BRUCH's theory — even after essential concessions and moderations — was far too specific to be ap-

plied with any ease on the Copenhagen school-children and their homes, which I got to know during my investigations. BRUCH's observations — however liberally interpreted — could have raised, at the most, the number of psychogenic adiposity cases in my material to 5 or perhaps 15, and that would minimize the difference with the rest of the cases so that there would no longer be any fundamental objection to entering all cases under this hypothesis which is now nearly unrecognizable. If, however, exact and unambiguous demands were made when applying BRUCH's theory particularly as to unmistakable maternal ambivalence (overfeeding cum overprotection combined with rejection) as well as eating-consolation and dependence in the child, then hardly one of the cases in question could be rightly termed a BRUCH constellation.

Most certainly were these children great eaters, but the same was mostly true about their mothers, fathers, brothers, sisters, and other relatives, and a great many of them were adipose like the patient. In my opinion it is an unbiological assumption that there should be fundamental differences in the etiology of obesity between children and adults; and though BRUCH thinks that she can prove essential traits common to all obese persons, young or old, she has not given much thought to the conclusions which it would be natural to draw from the co-existent occurrence of obesity in children and their family.

It is also indisputable that food mostly was of great emotional importance to the households, to which the obese children belonged. But hardly ever did my knowledge of these children and their kin allow me to accept BRUCH's assertion that food served as a likely *substitute* for love. I nearly always found that it was either an *expression* of love, or at any rate — when its emotional importance was less obvious — part and parcel of such non-pathological behaviour patterns in the members of the household as may be dependent upon traditions. This word is admittedly not very concise, and I shall try to define more accurately the semasiological convergence of ideas bearing on the problem before us.

As the upholder of life the meal has been imbued from times primeval with an air of sacrament. Special courses identify themselves with the great religious festivals: Easter lamb, St. Martin's goose, the Lent dishes, the English Christmas plumpudding, which all members of the family must stir, and which often contains objects of symbolic import (coins, rings, etc.). Solemnity is associated with the preparation of these courses and with the eating of them. The very lithurgical climax of the Christian religion is the Lord's Supper, where Bread and Wine is administered 'for then we spiritually eat the flesh of Christ, and drink his blood.' The daily bread is part of the Lord's prayer, to vilify it is sacrilege (cf. the folk-story about the girl who trod on the loaf). Many Danish farmers' wives still make the sign of the cross over

the new-baked loaf with the knife, before carving the first slice. Numerous primitive tribes give elaborate meat-offerings to the celestial powers. Similar phenomena can be found in most religions.

This sacramental tradition may be ever so threadbare in our modern civilization, it nevertheless runs in the blood of man that bread (i.e. food) is a 'gift of God'. And anyway, for many people the meal is still a sunny break in a drab day, in many small houses it is the only time when the whole family are gathered. Dinner is the focal point in the housewife's working-day; the preparation of the meal gives her the satisfaction of contributing her share in her allotted sphere — however dubious her dispositions may be seen in the light of dietary hygienics. The meal is one possibility of hers to bring happiness to the lives of those whose destiny is also her destiny for better or for worse; her husband and children perceive — and it is a gratifying feeling — that 'some one cares for them'. Father presides at table, and everybody must behave according to the rules; there is such a thing as table-manners, to observe them reflects honour on one self and on the house from which one is sprung. Toys are put away, singing or whistling isn't done; one must not leave the table before the meal is finished, so that the circle must not be broken.

When we consider food along these general lines we shall have to conclude that the meal is far from being a substitute for love, it is nearer the truth to call it a positive emotional action, and I think that hypothesis is a dangerous one, which blankly dismisses the idea.

But there are other psychical phenomena associated with the intake of food. The Danes have often been justly accused of attaching uncommon importance to food. The Iliad records to the praise of the Achaean heroes that they were moderate eaters and poured water into the wine. Our national Vikings were far from losing prestige on account of gluttony and intemperance. The Danish word '*madro*' has no equivalent in most languages, it literally means '*peace of meal*' and signifies how serious is the offence if one interrupts a person while he is having his meal. Other similar customs are typically Danish, but rarely found outside Denmark. In this country the guests are expected to compliment the hostess for her excellent cooking or for her exclusive taste in composing the dinner. In Denmark the hostess surveys the table to see that everybody has finished, she then rises and gives the signal to 'raise the table' by saying '*Velbekomme*'; the guests will all squeeze her hand and say, 'thank you for the food'. The word '*Velbekomme*' again is typically Danish (or Scandinavian); its literal meaning is 'well agree' i.e. 'may the food agree with you', but actually nobody thinks of this, the word having been reduced to being a polite sound, but essential in food manners in all classes. The word must be said whenever and wherever a person is encountered in the act of eating. The disturber of peace rehabilitates himself through the sincere wish

that the eater's digestive apparatus may prove equal to the task. This leads us to the popular ideas as to the quality versus quantity which are so frequently found in connection with the question of wholesome food. Many of these ideas are concerned with the necessity of eating much — and the food must be nourishing, too, which mostly means that it must be rich; again, it is desirable to be 'vigorous,' 'powerfully framed,' to have 'a reserve against lean days'; a great appetite is an infallible sign of good health; and so on and so forth. If we ask why adiposity is so widespread an illness in Denmark, I am convinced that we shall find the answer to our question in the conditions I have considered above. This, of course, by no means excludes (cf. my own material) that now and then we may find cases, when obesity is due to psychogenic, mostly acute, disturbances in the appetite regulation (eating-consolation) or to an inborn, remarkably great appetite. The few cases that I found had no peculiar 'family frame,' and my investigations permitted no conclusions as to the possibility that the eating-consolation should be caused by specific psychical impulse, or that it should be persons of a definable 'type' who react in this particular manner.

Summary

Accordingly my principal argument can be laid down as follows:

1) obesity in childhood must have an alimentary cause,

2) obesity in children seems to be *a not very specific manifestation*, provoked by such numerous incompatible and complicated psychological components as decide the attitude of the children and their surroundings concerning the taking and giving of food. Most important are the qualitative and quantitative dietary habits of the surroundings, and they are presumably founded on geography, ethnology, popular hygienics, and religion.

3) hence etiology should be sought in each separate case and therapeutic endeavours adapted accordingly; the latter probably aiming at nutrio-hygienic instruction of the child and its surroundings, plus psycho-therapeutic treatment in such cases where mental difficulties caused by obesity should require it.

4) Prophylactic measures against adiposity in childhood should presumably consist in intensified nutrio-hygienic education of the population generally.

Obésité psychogène dans l'enfance. III.

1. L'obésité dans l'enfance doit avoir une cause alimentaire. 2. L'obésité dans l'enfance semble *ne pas être une manifestation très spécifique:* elle est provoquée par de si nombreux facteurs d'incompatibilité et de complexes psychologiques, qui décident de l'attitude des enfants et de leur entourage, vis à vis de celui qui prend et donne la nourriture. Plus importantes, semble-t-il, sont les habitudes alimentaires qualitatives et quantitatives de l'entourage: celles-ci sont probablement fonction de la géographie, de l'ethnologie, de l'hygiène populaire, et de la religion. 3. Il s'ensuit que l'étiologie doit être recherchée dans chaque cas séparé, et les efforts thérapeutiques adaptés en conséquence. Ces derniers visent sans doute à des instructions d'hygiène alimentaire pour l'enfant et son entourage; un traitement psychothérapique doit s'ajouter, dans

les cas où des troubles mentaux provoqués par l'obésité le requéreront. 4. Des mesures prophylactiques contre l'obésité de l'enfance consisteront probablement à intensifier l'éducation de l'hygiène alimentaire de la population en général.

Über psychogene Fettsucht bei Kindern. III.

1. Fettsucht im Kindesalter muss eine alimentäre Ursache haben. 2. Fettsucht im Kindesalter scheint *eine nicht sehr spezifische Manifestation* zu sein, welche durch zahlreiche unvereinbare und komplizierte psychologische Komponenten — den Zustand der Kinder und ihrer Umgebung in Bezug auf das Nehmen und Geben der Nahrung betreffend — ausgelöst werden. Grösste Bedeutung haben die qualitativen und quantitativen Ernährungsgewohnheiten der Umgebung, welche vorwiegend geographisch, ethnologisch, volkshygienisch oder religiös fundiert sind. 3. Die Ätiologie sollte in jedem Einzelfall gesucht und die therapeutischen Bestrebungen dementsprechend angepasst werden. Die beste Hilfe ist ernährungshygienische Beratung des Kindes und seiner Umgebung und zusätzlich psychotherapeutische Behandlung in solchen Fällen, wo geistige Schwierigkeiten dies erfordern. 4. Prophylaktische Massnahmen im Kindesalter sollten hauptsächlich in einer verstärkten nahrungshygienischen Erziehung der Bevölkerung bestehen.

Sobre la obesidad psicogénica en los niños. III.

1. La obesidad infantil puede ser en la mayor parte de los casos de causa alimentaria. 2. Obesidades infantiles hay que pueden ser *una no muy específica manifestación*, provocada por numerosos componentes psicológicos incompatibles y complicados que deciden la actitud del niño y su medio ambiente en lo que concierne la administración de alimento. Mas importante son los hábitos dietéticos cualitativos y cuantitativos del medio alrededor del niño, los cuales están presumiblemente fundados en cuestiones geográficas, etnológicas, de higiene popular y de religión. 3. La etiología debe tratar de establecerse en cada caso particular y adaptar a ella las medidas terapéuticas, comprenderá también la necesaria instrucción de higiene-nutricional del niño y de su medi ambiente, además de las medidas psico-terapéuticas en casos que se presenten alteraciones de tipo mental condicionadas por la obesidad. 4. Las medidas profilácticas frente a la adiposidad infantil presumiblemente consisten especialmente en intensificar las medidas de higiene nutricional educacional de la población en general.

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Höyrups Allé 1
Hellerup. Denmark.

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From the Department of Child Health and the Department of Bacteriology, University of Manchester

Herpes Simplex

A Study of Complement-Fixing Antibodies at Different Ages

by A. HOLZEL, G. V. FELDMAN, J. O'H. TOBIN, and J. HARPER

Meningo-encephalitis occurs not infrequently in infancy and childhood but the exact aetiology is established only in a small proportion of cases. WALLGREN (1951) states that this condition can be caused by 11 different known neurotropic viruses, one of which is that of herpes simplex. The increasing number of cases of herpetic meningo-encephalitis reported in the past few years suggests that the virus of herpes simplex may be a more important aetiological agent than has been realised (SMITH *et al.* 1941; WENNER, 1944; ZARAFONETIS *et al.*, 1944; QUILLIGAN and WILSON, 1951; ALM, 1951). It is therefore necessary to include among the laboratory investigations specific tests for herpes simplex. Isolation of the virus does not suffice but needs serological or histological confirmation. Until recently the serological diagnosis has been determined by the serum neutralisation test in mice or on the chorio-allantois of the developing chick embryo. As these tests require many animals or eggs if a significant rise of titre is to be demonstrated, a simpler in vitro test is preferable. BEDSON (1929) showed that a complement fixing antigen could be made from the foot pads of infected guinea-pigs, but no further methods of antigen preparation were reported until HAYWOOD (1949), DUDGEON (1950) and ALM (1951) used infected chick embryo antigens in the detection of herpes antibodies.

There have been but few studies of the antibody level in the blood of infants and children and in these only the neutralisation test has been used. DODD, JOHNSON and BUDDINGH (1938) and BURNET and WILLIAMS (1939) showed the relationship in infants between herpes simplex and aphthous stomatitis. Once infected, an individual always carried the virus and had antibody in the serum. ANDERSON and HAMILTON (1949) showed that neutralising antibody was transmitted from mother to infant but that it disappeared by 7 months in the majority of cases. These workers considered that this antenatally transmitted immunity, although undetectable by the serum neutralisation test, persisted between this age and the onset of primary infection

which occurred, in their series, between the ages of 1 and 2 years, or less likely that some "intrinsic genetically determined resistance of the tissues to infection" was present during the first year of life.

It has been generally assumed that the vast majority of infants are protected from infection during their first year and that herpes is only possible in those children whose mothers have no antibody in their serum.

This present study was conducted to dermine the distribution of complement-fixing antibody at different ages and to try to evaluate the complement fixation test using an egg antigen in the detection of herpes simplex antibody.

Sera were obtained for this purpose from (a) the umbilical cords of infants delivered in a large maternity unit, (b) babies attending a welfare clinic, (c) babies and children admitted to hospital on account of various diseases and (d) from adults who were patients in hospitals or attending out-patient departments.

Technical Methods

Preparation of antigen

Antigen was prepared from the chorio-allantois by the following method. Twelve-day old developing chick embryos were inoculated on the chorio-allantois with a dose of herpes simplex virus suspension giving a confluent growth of pocks after 48 hr. incubation. After this time the eggs were placed in the ice-box at 4° C for 1—2 hr. before the infected portion of the chorio-allantois was harvested. The membranes were ground in a pestle and mortar with sand; 0.5 ml of normal saline containing 10 % Hartley broth was added for each membrane used. The whole was transferred to a centrifuge tube and allowed to stand at room temperature for 2—3 hr. It was then placed in a refrigerator at —30° C until required. For use the suspension was thawed and spun at 2500 r.p.m. for 10 min. in a horizontal centrifuge and the supernatant removed. This was then centrifuged at 6000 r.p.m. in an angle machine for 20 minutes and the supernatant of this centrifugation was used as the herpetic antigen.

Preparation of normal control antigen

Antigen was prepared from normal chorio-allantoic membranes of fourteen-day old chick embryos by the same method as described above. Before use it was titrated against a serum containing non-specific antibodies in order to determine its effectiveness in demonstrating non-specific fixation.

Preparation of antisera

Sera were inactivated at 56° C for 1/2 hr. and if found anti-complementary in the screening test (see below) were inactivated for a further half hour at 56° C.

Technique of complement-fixation test

The dilution of antigen used in the test was determined by a chess board titration using two-fold dilutions of antigen and immune sera. The antigen prepared as above was usually satisfactory when employed at a dilution of 1/8 to 1/16. A preliminary screening test was done using herpes antigen only and sera diluted 1/2. All positive

sera were then titrated to a dilution of 1/64 and the first dilution was also tested with normal chorio-allantoic antigen diluted to the same degree as the herpes antigen. A standard antiserum was included in all tests. The normal egg-membrane antigen was tested with a serum containing non-specific antibodies in order to control its effectiveness in denoting these reactions.

The 5 × 0.2 ml volume test was used. Guinea-pig serum was used as the source of complement and was diluted to give 2 M.H.D.'s per unit volume. Fixation was allowed to proceed for 18 hr. at 4° C and then sensitised cells (2 % sheep cells and 5 M.H.D. haemolysin) were added and the results read after incubation in a water bath for 30 minutes. Serum end points were taken as those showing + + + + (100 %) or + + + (75 %) fixation.

Technique of neutralisation test

The method introduced by BURNET and LUSH (1939) was used as follows:

Undiluted inactivated serum was mixed with virus diluted to give approx. 500 pocks per membrane when 0.05 ml of a negative serum and virus mixture was inoculated onto the chorio-allantois of four 12-day old chick embryos. All the sera tested gave either less than 30 % or over 95 % reduction in the number of pocks obtained after 48 hr. incubation. The negative sera almost certainly gave a reduction much less than 30 % but there was difficulty in making an exact count if 300 or more pocks were present on one membrane. Some pocks coalesced with their neighbours and the exact number could not be determined. With less than 500 pocks per dose a series of 4 eggs often showed no pocks when mixed with positive serum.

Discussion of technical methods

Before the majority of the sera were tested a comparison was made between the results obtained by the neutralisation and complement fixation tests. They were also compared with those obtained by HAYWOOD and DUDGEON as shown in Table 1. Of the seventy-nine sera tested two gave non-specific fixation with normal chorio-allantoic antigen and were excluded from the table. Neither contained neutralising antibody. A close correlation between the two tests was evident, although two sera which were negative by complement fixation contained neutralising antibody.

The complement fixing antigen, prepared as described, was not completely satisfactory as seventeen non-specific reactions occurred with the control egg antigen. These reactions were distinct for non-specific reactions due to positive Wassermann sera.

Attempts to grow the strain of herpes virus that was used throughout this work in the amniotic and allantoic cavities met with irregular results. Non-specific reactions are very uncommon with allantoic fluid (HENLE *et al.*, 1948), and this type of antigen would obviously be advantageous. Absorption of serum with sheep red cells as recommended by these workers was not satisfactory except in cases of glandular fever. DUDGEON recommended inactivation of sera at 62° C for 15 min. As two out of four sera inactivated at this temperature showed a marked fall in their antibody level this method was not employed.

The non-specific factor in egg membrane was removed completely by extraction with acetone and ether (CASALS, 1949) and reduced by the addition of chloroform (HOYLE, 1948), but both methods, especially the first, reduced the yield of herpes antigen. Further work on the preparation of a more satisfactory antigen is proceeding.

TABLE 1

Comparison of Complement Fixation and Neutralization Tests.

	(A) Sera positive by neutralization test — Complement fixation tests		(B) Sera negative by neutralization test — Complement fixation tests	
	+ ve	− ve	+ ve	− ve
HAYWARD (1950)[1]	75	1	0	19
DUDGEON (1950)	30	0	0	10
HOLZEL *et al.*	52	2	0	23

[1] Infected allantoic or amniotic fluid used as antigen.

Results of Survey

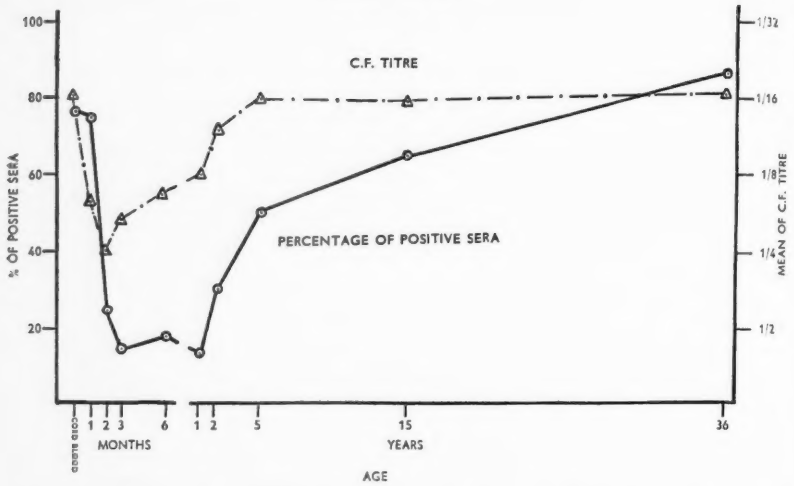
In all, 325 sera were tested. Twenty-one were not included in the survey; 17 of these reacted non-specifically with normal antigen and 4 were strongly anti-complementary and not affected by heating at 56° C for one hr. Twenty-one other sera which were anti-complementary on preliminary screening had this effect removed by a further heating at 56° C for 1/2 hr.

The results of the survey of the 304 sera are shown in Table 2 and in the Figure.

TABLE 2

Distribution of Complement Fixing Antibodies at Different Ages.

Age group	Total number of sera tested	Number of positive sera	Number of negative sera	% positive	Complement fixing titre of positive sera						Mean titre of positive sera
					1/2	1/4	1/8	1/16	1/32	1/64	
Cord blood	41	32	9	78	0	3	5	11	13	0	1/16.7
0–1 months	13	10	3	77	0	4	5	1	0	0	1/6.5
1–2 »	8	2	6	25	1	0	1	0	0	0	1/4
2–3 »	29	4	25	14	0	2	2	0	0	0	1/5.7
3–6 »	35	6	29	17	1	1	3	0	1	0	1/7.1
6–12 »	30	4	26	13	1	1	0	1	1	0	1/8
1–2 years	44	13	31	30	0	3	2	3	5	0	1/13.6
2–5 »	28	14	14	50	0	1	2	7	4	0	1/16
5–15 »	41	26	15	63	0	1	7	11	6	1	1/15.7
Over 15 years .. (Average age 36 years)	35	30	5	86	0	1	4	16	9	0	1/17.1



From the results obtained it can be seen that the percentage of positive sera was highest in the adult population and in the cord bloods. During the newborn period the percentage of positives remained high but the mean titre showed a marked fall, indicating a rapid loss of antibody during this time. The number of positive sera fell in the second and third months of life and remained low until the end of the first year. A rapid rise in the percentage of positives took place during the second year and continued more slowly until adult life, indicating that primary herpetic infection though predominantly occurring in children is also found in adults (ALM, 1951; KILBOURNE and HORSFALL, 1951). The mean titres showed a rise until the end of the second year after which they remained at about the adult level. The positive sera between three and twelve months were obtained from infants who had still retained some maternal antibody and from those who had acquired a primary infection. The majority of children had lost all complement fixing antibodies by the end of the second or third month, as shown in Table 3 in which the level of the mothers' antibody is compared with that of their infants during the first three months of life. That the majority of the 54 negative infants between 3—6 months started life with antibody was shown by the fact that seven of eight mothers sampled at random had herpes antibody in their serum. The sera of mothers of seven of the children aged 3—5 months, who had antibody present, also gave a positive complement fixation test. However, two of these infants, one of whom had a herpetic stomatitis at the age of 14 weeks, showed rising titres of antibody indicating primary infection. In the other five cases no conclusion could be drawn as to whether the antibody present was maternal or actively acquired.

TABLE 3

13 Cases Investigated for Fall of Maternal Antibody after Birth.

Case no.	Mother's complement fixing titre	Age of baby (weeks)	Babies complement fixing titre
1	1/32	4	1/4
		6	< 1/2
2	1/16	1	1/16
		4	1/4
3	1/16	4	1/4
4	1/16	3	1/8
		6	1/2
5	1/32	5	< 1/2
6	1/16	4	< 1/2
7	1/16	11	< 1/2
8	1/8	11	< 1/2
9	1/16	11	< 1/2
10	1/32	10	< 1/2
11	1/32	18	< 1/2
12	1/8	10	< 1/2
13	1/16	4	< 1/2

Discussion

These results indicate that the complement fixing antibodies follow the same general trend as herpes neutralising antibodies as shown by ANDERSON and HAMILTON (1948). It was found that complement fixing antibodies disappeared earlier, perhaps because complement fixation was less sensitive than the neutralisation technique in discerning small levels of antibody. Human sera diluted in the range used in the complement-fixation test all gave more than 95 % neutralisation but if the dilution was carried a little further, percentage neutralisation fell off very rapidly. This is similar to the effect of dilution of serum in the case of vaccinia antibody reactions using the chorio-allantoic method (KEOGH 1936). The end-point by complement-fixation is therefore probably not far removed from the end-point obtained by the neutralisation test in which neutralisation of less than 75 % means that only negligible amounts of antibody are present. Several of the cases of herpetic encephalitis have occurred at an early age. The case reported by SMITH *et al.* occurred in a four-weeks old infant. Kaposi's varicelliform eruption, which in young children is mostly a primary herpetic manifestation, is reported often in the first year of life. Such cases have been reported by WENNER (1944) and by BRAIN and DUDGEON (1951). We have seen three cases between

five and nine months, from two of which the virus of herpes simplex was isolated and, in another, serological evidence indicated infection by the same agent. Three cases of herpetic stomatitis in babies under one year have also been seen, the youngest being six weeks of age. In another case of stomatitis in a $3\,^1/_2$ month old infant the mother had herpetic antibodies in her serum. A rising titre of antibodies during his illness showed that the baby was experiencing a primary infection and that he had lost its maternally transmitted antibody and immunity by this age. Two of the cases of herpetic stomatitis seen in children under 1 year were discovered on routine examination, not having been noticed by the mother nor having produced apparent discomfort in the infants, supporting the supposition that much primary infection is sub-clinical.

The sera from three cases of recurrent herpes were followed from six months to two years and no variation in complement fixation titre, was found. This is in agreement with the results of the neutralisation test and with the findings of DUDGEON (1950). However ALM found that in 3 cases of encephalitis the complement fixing antibodies had fallen or disappeared after three months. In one case of herpetic encephalitis, antibody, after the initial rise, remained at the same level for the next six months; it was not followed further. Sixteen paired sera from chronic herpetics taken at intervals of ten days to one month all gave the same titre.

As meningo-encephalitis is known to follow either an overt or sub-clinical infection with herpes, investigation in this syndrome should include examination for herpes antibody. The complement fixing antibody does not appear until the end of the second or beginning of the third week following symptoms and continues to rise until the fifth or sixth week. It should therefore be possible to make a serological diagnosis in those cases in which encephalitis is a late manifestation of herpetic infection.

From these findings it appears that most children are born with herpetic antibody which they lose within 3 months. Infection with herpes simplex virus can occur at any time during life but is most common in the early years of childhood, as has been stressed by BURNET (1945). The complement fixation test is useful in the detection of herpes simplex but when used in the diagnosis of individual cases, especially in those of meningo-encephalitis. the results should be confirmed by the neutralisation test.

Summary

1. A study of antibodies to herpes simplex virus in different age groups has been made, using the complement fixation technique. Antigen derived from the chorioallantois of the chick embryo is evaluated.

2. Passively transmitted maternal antibodies disappear in the majority of infants in the course of the second and third month of life. These infants are then probably susceptible to primary herpetic infections.

3. The rapid rise in the percentage of positive sera from the second to the fifth year of life indicates the period during which primary infections most commonly occur.

Herpès simple. Etude des anticorps par fixation du complément aux différents âges.

L'étude des anticorps vis-à-vis du virus de l'herpès aux différents âges a été faite grâce à la technique de la fixation du complément. L'antigène dérive de la membrane chorio-allantoïdienne de l'embryon de poulet. Transmis de façon passive, des anticorps maternels disparaissent chez la majorité des enfants dans le cours du 2e ou 3e mois de la vie. Ces enfants sont alors seulement susceptibles de réaliser une infection herpétique primaire. L'élévation rapide du pourcentage de réaction positive de la 2e à la 5e année de la vie indique la période pendant laquelle les infections primaires apparaissent le plus communément.

Herpes simplex. Eine Studie der komplementbindenden Antikörper in verschiedenen Altersstufen.

Eine Studie der Antikörper gegen das Herpes simplex-Virus in verschiedenen Altersstufen wurde durchgeführt; verwendet wurde die Komplementfixationstechnik. Das Antigen stammte von der Chorioallantois von Hühnerembryonen. Passiv übertragene mütterliche Antikörper verschwinden meist im Laufe des zweiten oder dritten Lebensmonats des Kindes. Diese Kinder sind dann wahrscheinlich empfänglich für die primäre Herpes-Infection. Der rapide Anstieg des Prozentsatzes positiver Seren vom zweiten zum fünften Lebensjahr zeigt die Periode der häufigsten Primärinfektion an.

Herpes simple. Estudio de los anticuerpos fijadores del complemento a las diferentes edades.

Se ha hecho un estudio sobre los anticuerpos frente al virus del herpes simple en grupos de edades diferentes, usando la técnica de fijación del complemento. Se ha evoluado el antigeno derivado de la membrane corioalantoidea del embrión de pollo. Los anticuerpos maternos transmitidos pasivamente desaparecen en la mayoria de los niños en el curso del 2° o 3° mes de la vida. Estos niños son entonces probablemente susceptibles frente a infecciones herpeticas primarias. El rápido aumento en el porcentaje de sueros positivos del 2° al 5° año de la vida indica el périodo durante el cual las infecciones primarias ocurren mas conmunmente.

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St. Mary's Hospital
Whitworth Park
Manchester 13. England.

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From the Pediatric Clinic of the Municipal University of Amsterdam and from the Bacteriological Laboratory of the Department of Public Health of the City of Amsterdam

Diarrhoea in Infants and Its Relation to a Certain Type of Colibacteria

by MARIE R. H. STOPPELMAN and A. B. J. VAN DER PLAATS

There is still much difference of opinion as to the aetiology of the so-called infantile diarrhoea. The question may be asked if it includes various diseases, each with a different pathogenic agent. The mortality of epidemics of infantile diarrhoea varies.

In contrast with the serious gastro-intestinal symptoms, at autopsy no, or only slight changes are found in the intestinal tract (4, 13, 41). Sometimes there was slight hyperaemia of the mucosa, occasionally some erosions. The mesenteric lymphglands may be enlarged.

In spite of several shortcomings, the number of epidemics of infantile diarrhoea in the Netherlands in hospitals and maternity homes is, fortunately, small, apart from the big epidemics during the last year of the war, especially from the end of 1944 to September 1945. This epidemic was not at all restricted to newborns, neither to infants nursed in hospitals.

As mentioned before, there is difference of opinion as to the cause of the epidemic diarrhoea of infants. In the diarrhoea of the neonates, amongst others the possibility was considered whether the penetration of the intestine by bacteria sterile until after birth, might be the cause of the diarrhoea.

In the course of the years various micro-organisms have been considered as a probable cause; amongst others Proteus (53), Klebsiella (42, 45), Pseudomonas aeruginosa (55), Lamblia (30), Monilium (34) etc.

In 1935 epidemics were mentioned, in which certain special strains of colibacteria were considered to be the causes of the diarrhoea. During an epidemic at Memphis colibacteria were isolated which slowly fermented lactose and had the same antigenic structure (16). At Toronto the isolated strains had certain biochemical properties (33). In 1943 BRAY (6, 7) found that in the faeces of infants with severe diarrhoea a certain type of colibacteria was present in 95 % of the cases investigated. In the control group this type was only found in 4 %. An investigation in 1945 yielded the same results. BRAY called the strain: Bact. coli neapolitanum.

In numerous epidemics this same type of colibacteria was found in a varying percentage (30, 36, 53). In the Netherlands BEEUWKES c.s. (4) showed that colibacteria of this type also occur in this country. Several of these isolated strains were further examined by KAUFFMANN (34) for their biochemical and antigenic properties. KAUFFMANN had 34 strains sent to him from England, the Netherlands and Denmark. Among these three types were found two of which had identical somatic and capsule antigens, but different flagellar antigens, viz. OIII, B4 (H2) and OIIIB4HI2. Also the faeces in severe diarrhoea have a typical characteristic smell. The other type was: O55, B5H6.

It is an established fact that at least in a great number of cases of diarrhoea colibacteria of the first two types are present in the intestine and predominate over the other types of colibacteria.

Should an aetiological relation be assumed between the epidemics of severe diarrhoea in infants and these special colibacteria? The various investigators do not agree about this. In KAUFFMANN's opinion the colibacteria of the above-mentioned types may cause diarrhoea in infants, but still other types may prove to be important. GILES and SANGSTER do not say anything definite about it. TAYLOR *et al.* are not sure that this type of colibacteria is of aetiological importance, no more than ROGERS c.s. or WILLIAMS and LAURELL c.s. HOLZEL *et al.* found a greater percentage of E. coli type Bray Giles in cases with infantile diarrhoea with a serious course than in the more benign cases. According to BEEUWKES and contributors these facts argue in favour of the aetiological importance of these colibacteria in diarrhoea of infants.

KIRBY *et al.*, who made an investigation during two epidemics in a maternity home at Manchester, attribute the first epidemic to infection with E. coli type Bray Giles. Of 37 infants, who had colibacteria of the type Bray in their faeces, 30 fell ill. That not all the children fell ill is not against his conception. When there is infection with Salmonella and Shigella, all the infected persons do not necessarily become ill.

The fact that in some epidemics of diarrhoea in infants viruses probably play a part (9, 39, 61), need not contradict the conception that E. coli type Bray-Giles may cause severe diarrhoea. For the diagnoses serious diarrhoea and intoxication are syndromes and not aetiological diagnoses. Various facts, however, are to be found in literature which make it improbable that colibacteria of the type Bray-Giles have an aetiological significance.

In the article by KIRBY *et al.* in which these authors try to make it clear that E. coli type Bray-Giles was the cause of one epidemic, the pros and cons are not discussed in detail. In ward A of the maternity home, 30 of the 37 infants who had colibacteria of the type Bray-Giles in their faeces fell ill. In ward B, there were 4 infants with this type of colibacteria in their faeces without symptoms. Five weeks after the end of the epidemic 9 more infants were found to have positive faeces-cultures; but none were ill.

Although all infants infected with this bacterium do not develop diarrhoea, it is strange that not a single child of this group became ill. As well as this the latter 9 infants were all prematures, which increases the chances of developing the disease. GILES and SANGSTER mention that in a crèche where 12 infants had dysentery (Sonne), 5 of these infants had E. coli type Bray-Giles. They considered this as a mixed infection. The question arises whether the conditions in the intestine had changed in such a way that the colibacteria of this type could predominate.

In a children's home PAYNE and COOK investigated the faeces of 60 infants for one year. In 17 infants colibacteria of the type Bray-Giles were found, and only 5 had diarrhoea. At one time 10 of the 15 healthy infants had this type of colibacteria in their faeces without an ensuing epidemic.

We wanted to investigate if an aetiological relation could be shown between severe diarrhoea and this type of colibacteria. This seemed only possible through a systematic epidemiological investigation.

Method

The faeces of each infant admitted to the Children's Clinic were cultured three times for E. coli type Bray-Giles. The faeces of all the children nursed in the two infant-wards were cultured once a week. At each culture 20 colonies of colibacteria were agglutinated with serum[1] by the object-glass method and the positive strains were kept. These strains were examined biochemically and antigenically. As the colonies examined were taken at random, it was possible to prove to what extent the colibacteria of the type Bray-Giles had ousted other bacteria. The biochemical properties of the strains isolated on endo-medium were examined. All strains were gramnegative and had the same properties as E. coli and gave a positive methyl red reaction. Fifty-two of the seventy-two strains were mobile. The reaction of VOGES and PROSKAUER was positive except in one case. Five strains did not ferment saccharose; no fermentation occurred in the three weeks of incubation. The strains did not haemolyse sheep erythrocytes. The mean titre of agglutination with specific antiserum was 1:1000. By crossabsorption with the method of CASTELLANI proof was obtained, that the isolated strains were identical with those mentioned by BEEUWKES. No typhoid antigen could be demonstrated. Some strains were sent to Dr. F. KAUFFMANN,[2] for typing.

Clinical and Bacteriological Findings

This investigation was continued for 11 months, viz. from September 1949 to August 1950. In the first 3 months 16 infants had diarrhoea, which in some cases was present on admission, in others appeared during the stay in hospital. These infants had no bacteria of the type Bray-Giles in their faeces. In that period there were 2 infants in whom 1 and 2 colonies were positive respectively out of 20 colonies that were examined. At the following examina-

[1] Our thanks are due to Dr. H. BEEUWKES for his help and his kindness to provide us with type specific serum.

[2] We are very much indebted to Dr. F. KAUFFMANN for his valuable help.

tion, a day later, the cultures were negative. These 2 infants were nursed in different wards. Moreover, the latter infant was admitted when the faeces of the former had already been negative for a few weeks.

In the beginning of December 1949 an infant which had been in the clinic for three weeks and whose faeces had repeatedly been negative, developed diarrhoea. The faeces contained colibacteria of the type Bray-Giles; 80 % of the colonies agglutinated. The examination of the faeces of the other infants, as well as of the nurses and doctors who worked in the infant-ward, was negative. Infection, e.g. via fruit-juice, can never be totally excluded.

On December 12th an infant with severe diarrhoea was admitted; 80 % of the colonies of colibacteria yielded positive agglutination. On December 26th an infant was admitted with diarrhoea and colibacteria of the type Bray-Giles in its faeces. This child came from a chiidren's home. Infants from that home as well as their mothers and nurses were examined. Of the 11 infants 5 had diarrhoea. Two of them had colibacteria of the type Bray-Giles, of one the colibacteria had auto-agglutination, of one the faeces was sent in too late and one had no colibacteria of this type in its faeces. One of the healthy infants had 20 colonies which were positive. It is remarkable in this epidemic, which occurred within one week, that one sick infant did not show colibacteria of the type Bray-Giles.

During the 11 months the faeces of 210 infants admitted to the Children's Clinic were examined regularly. 27 infants with diarrhoea had colibacteria of the type Bray-Giles in their faeces; in 25, 80 to 100 % of the 20 colonies investigated agglutinated; in 2 infants this percentage was 40 % and 50 % respectively. In 11 of this group the faeces were already positive when they were admitted. The other 16 infants had no colibacteria of the type Bray-Giles in their faeces during the first few days, they had no diarrhoea, but only developed diarrhoea later, and at the same time this type of colibacteria in their faeces. Colibacteria of the type Bray-Giles were found in the faeces of 24 infants who did not develop diarrhoea. In 12 of them 80 to 100 % of the colonies yielded positive agglutination. In the other 12 infants this percentage was smaller. Six of these 24 infants had diarrhoea first. At the time when colibacteria of the type Bray-Giles were found for the first time, the diarrhoea had much improved or was already cured in 5 cases. The sixth child was admitted with severe diarrhoea. The child had already been ill for ten days before admission. From the faeces, colibacteria of the type Bray-Giles were cultured only on the third day; the culture was negative during the first two days. The appearance of E. coli type Bray-Giles in the faeces did not concur with the symptoms becoming more severe, though no improvement could be detected in the first four days.

The great number (12) of infants in whom 80 % to 100 % of the colonies of colibacteria were of the type Bray-Giles and who did not develop diarrhoea is worth noting.

One of these infants, who had a positive culture and did not develop diarrhoea, was a child of 12 days, which had been admitted in a serious condition on account of a serious umbilical haemorrhage. The child could be kept alive by immediate blood transfusion. In such a young infant, weakened, moreover, by the great loss of blood, one might expect diarrhoea to arise if the child had been infected by a pathogenic bacterium. The 6-year-old sister also had colibacteria of this type in her faeces, all the colonies yielded agglutination. The mother of one of the infants from the Children's home had a few positive colonies on the plate. For the rest, all examinations of the contacts were negative.

Discussion and Conclusions

In this period of 11 months of the 210 infants there were thus:

33 infants with diarrhoea without colibacteria of the type Bray-Giles in their faeces;

27 infants with diarrhoea, with this type of colibacteria in the faeces;

18 infants who did not develop any diarrhoea and whose faeces contained these bacteria;

6 infants who first had diarrhoea and in whom later the faeces became positive without a relapse arising.

It is possible that under certain circumstances and especially with diarrhoea, predomination of this type over the colibacteria of other types is promoted.

The following argues against the aetiological significance of E. coli type Bray-Giles:

1. That the faeces of an infant with diarrhoea during an explosive epidemic in a home were negative, while the faeces of the other sick infants were positive.

2. Positive results show 24 infants in the Children's Clinic without diarrhoea, against 27 infants with diarrhoea out of a total number of 210 infants.

3. That all or nearly all colonies of E. coli investigated were positive in 12 infants without diarrhoea, among whom there was one very young infant who was admitted in a very bad general condition.

4. That 6 cases were found in which diarrhoea arose firstly and E. coli type Bray-Giles only appeared later in the faeces, as against other positive cases where these bacteria could be shown immediately at the onset of the diarrhoea.

Summary

The literature is surveyed. An epidemiological investigation on the incidence of E. coli type Bray-Giles in infants, in the Children's Clinic of the University of Amsterdam is described. No proof was obtained in this investigation, that E. coli type Bray-Giles is not pathogenic. There are however several facts, which argue against the aetio-

logical significance of this type E. coli in infantile diarrhoea. It is suggested, that special circumstances may favour the predominance of this type of coli bacteria in the intestine.

La diarrhée infantile et ses rélations avec un certain type de colibacilles.

Les résultats d'une investigation épidémiologique concernant la présence d'E. coli type Bray-Giles en nourrissons admis dans la Clinique Infantile de l'Université d'Amsterdam sont présentés. Il n'est pas démontré qu'E. coli type Bray-Giles est non-pathogène. Cependant des différents faits contredisent le rôle étiologique de ce type d'E. coli. Il est considéré, si des changements du milieu intestinal puissent faire prédominer E. coli type Bray-Giles dans les intestins.

Diarrhoe bei Kindern und ihre Beziehung zu bestimmten Colibakterientypen.

Beschrieben wird eine epidemiologische Untersuchung über das Auftreten der Colibakterien vom Typ Bray-Giles bei Kindern in der Universitäts-Kinderklinik Amsterdam. Bei dieser Untersuchung konnte kein Beweis dafür erbracht werden, dass Colibakterien vom Typ Bray-Giles nicht pathogen sind. Es gibt allerdings einige Tatsachen, die gegen die ätiologische Bedeutung dieses Colityp bei der kindlichen Diarrhoe sprechen. Es wird die Vorstellung vertreten, dass besondere Umstände das Vorherrschen dieser Colibakterien im Darm begünstigen können.

Diarrea infantil y sus relaciones con ciertos tipos de bacterias coli.

Se describe una investigación epidemiológica sobre la frecuencia del coli tipo Bray-Giles en niños estudiados en la clínica pediátrica de la Universidad de Amsterdam. No ha podido obtenerse en esta investigación una prueba evidente de que el coli tipo Bray-Giles no sea patógeno. Hay sin embargo varios hechos los cuales hablan en contra de la significación biológica de este tipo de coli en la diarrea infantil, y se sugiere que especiales circunstancias pueden favorecer el predominio de colis de este tipo en el intestino.

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Central Institute for Nutrition Research T.N.O., Utrecht — Wilhelmina Children's Hospital, Utrecht — Juliana Children's Hospital, The Hague

Coeliac Disease

IV. *An Investigation into the Injurious Constituents of Wheat in Connection with their Action on Patients with Coeliac Disease*

by J. H. VAN DE KAMER, H. A. WEIJERS and W. K. DICKE

In some of the previous articles (5, 6, 12, 13) it has been shown that wheat flour has a harmful effect on patients with coeliac disease. On being given wheat flour, the patients deteriorate clinically, possibly even leading to a crisis, while the fat excretion in the faeces increases considerably in this period. At the same time, however, it appeared that wheat starch (= Amylum tritici), like rice flour, potatoes and maize flour, had no harmful influence, while the fat excretion in the faeces did not alter (5). This is contrary to the opinion of ANDERSON (1) and SHELDON (9), who considered that *all* starch-containing foods must be avoided. Afterwards however SHELDON (10) has confirmed our results.

Since we could find no sign of any harmful effect of the carbohydrates of wheat, it was necessary to discover which constituent of wheat caused this effect.

For this purpose various fractions were prepared from the same wheat as that used in the previous experiments (Dutch wheat, consisting of a mixture of the varieties Staring, Koga, Alba and Minister, extraction degree about 72 %, ash content calculated on dry substance 0.60 %). The following fractions were prepared:

1) *Gluten.* A dough was prepared by kneading, and by further kneading under running water, the starch was washed out and the gluten remained (100 g wheat = about 7 g gluten).

2) *Gluten washwater.* The washwater used in the gluten preparation was collected. This washwater contains the water soluble proteins, including a fraction of the gliadin (washwater A). To prevent any dissolving of gliadin, another sample of flour was washed with a 10 % solution of NaCl (BAILEY, 4) in which gliadin is insoluble. After removing the starch by centrifuging, the washwater thus prepared contains practically no gliadin (washwater B).

3) *Gliadin and glutenin.* The gluten, prepared by kneading with NaCl 10 %, was further differentiated into gliadin and glutenin by shaking with ethanol 50 % for 3 hours at room temperature (BAILEY, 4). By this means the gliadin dissolves, while the glutenin remains. The ethanolic gliadin solution was diked at 50—55° C and the

residue ground. Although the gliadin and glutenin thus obtained are not pure, this simple method was preferred for a tentative differentiation of the wheat-proteins.

Later it appeared simpler to prepare the gliadin without previous removal of the starch, by extracting the wheat flour (after extraction with NaCl 10 %), by shaking directly with ethanol 50 % for 3 hours at room temperature (100 g wheat = about 7 g gluten = about 3.75 g gliadin).

Analysis of the gliadin:

starch and sugar	— absent
"fat"	— trace
protein	— ca. 95 %
water	— ca. 5 %.

4) *Ash.* Prepared by ashing wheat flour at 500° C.

5) *Crude fibre.* Prepared according to SCHARRER-KÜRSCHNER (8).

6) "*Fat*". The flour was extracted twice with boiling ethanol 96 %, and once with boiling ether. After distilling off the collected extracts, the residue was extracted a few more times with ether. Finally the ether was distilled off and the remaining fat, mixed with some glucose, was dried in vacuo over P_2O_5.

Experiments

To test all these fractions in the usual way on patients with coeliac disease (5) would take a long time. Since one of the patients with coeliac disease happened to show an abnormally violent reaction to the administration of any form of wheat — 3 to 6 hours after administration, severe abdominal pain, vomiting, pallor and sometimes even slight signs of shock — the action of the various wheat fractions was first investigated with this patient, the severe clinical symptoms serving as an indicator.

Unfortunately it was impossible to check her reactions also by chemical means, since for this purpose, it would have been necessary to give the various diets for longer periods, which would not have been tolerated by this quickly and strongly responding child. No hypersensitivity was noticeable, however, after intracutaneous injections of wheat extracts.

This patient Mechie (♀, born 19.8. 1946), with whom the investigation was carried out, had already been two years in the Wilhelmina Children's Hospital in Utrecht. She had a typical coeliac history and on examination complained with all the criteria necessary for diagnosis of idiopathic coeliac disease (13). She responded well to a diet rich in milk protein. Her reaction to wheat was so violent that even a small piece of rusk or biscuit caused vomiting, abdominal pain etc. within a few hours.

Testing the various wheat fractions gave the following results:

The acute reaction to administration of wheat has already been mentioned, but just as with other coeliac patients, with Mechie also not a single reaction was observed after consuming *wheat starch.*

Neither was any reaction seen after administering the *ash*, the *crude fibre* and the *fat-fraction*, each prepared from twice the amount of wheat

which in her case caused acute abdominal pain, vomiting and slight signs of shock.

A distinct positive reaction was caused by *gluten*. With further differentiation of the gluten, *gliadin* was seen to cause a severe reaction, while the reaction to *glutenin* was much less.

The *gluten washwater A* gave a slight reaction. *Gluten washwater B*, prepared by washing with a 10 % NaCl solution, gave no reaction at all.

Subsequently, the gluten and the gliadin fraction were tested in the usual manner (5) on coeliac patients who react less violently, and in their cases the fat excretion was used as an index in addition to the clinical symptoms. Because it had been observed several times in Mechie's case that the glutenin fraction, in contrast to the gliadin fraction, only caused a slight reaction, it was not investigated further for the present.

Influence of gluten

The diet used for the young patients Hendrika and Robert — with or without the addition of 14 g gluten (this amount tallies with 230 g wheat) — consisted of: 750—800 ml cow's milk, 10 g sugar, 50—65 g glucose, 100 g vegetables (carrots, stewed apples, or endive), 40—50 g lean meat, 17 g butter fat, 1 egg, 100 g apple juice, 100 g apple; starch-containing nutrients, included potatoes, maize starch, wheat starch and wheat flour, a total of 70—100 g starch. Sometimes the three first-named products, whose harmlessness has already been shown (5) were exchanged on the basis of their starch content.

Gluten was added to the diet in the form of small buns, baked with wheat starch, yeast, glucose, salt and water.

The daily fat excretion of two patients is plotted in figures 1 and 2.

The patient, Hendrika (♀, born 19.2. 1946) had already been a few years under treatment at the out patients of the Juliana Children's Hospital at The Hague; typical coeliac history; sensitive to wheat. Height at commencement of trial period 98 cm, weight 15.6 kg.

The patient, Robert (♂, born 27.6. 1945) had been in the Juliana Children's Hospital in The Hague for two months; typical coeliac history; sensitive to wheat. Height at beginning of trial period 95 cm, weight 14 kg.

From the two figures 1 and 2 it appears that gluten causes the same harmful effect as wheat flour.

Influence of gliadin

The diet used by the three following patients (Prudent, Maryan and Toos) — with or without the addition of 3—5 g gliadin — consisted daily of: 3 times porridge of 200—275 ml albuminous milk (5.5 % butter fat) with 75—

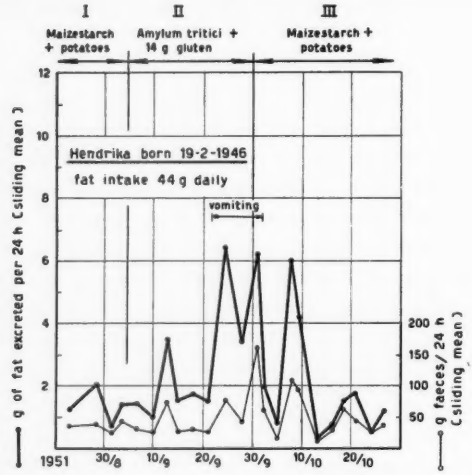

Fig. 1. Excretion of fat in the faeces when on diets containing respectively, maize-starch + potatoes, amylum tritici + gluten and maize-starch + potatoes.

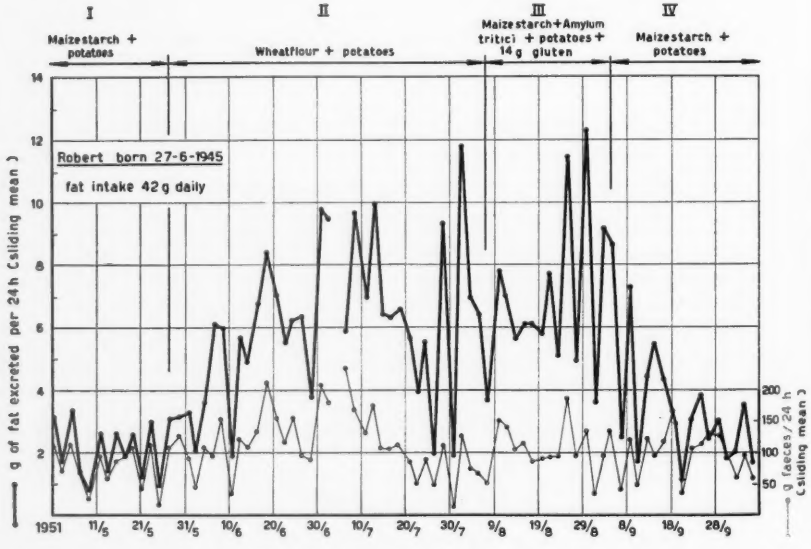

Fig. 2. Excretion of fat in the faeces when on diets containing respectively, maize-starch + potatoes, wheat-flour + potatoes, maize-starch + amylum tritici + potatoes + gluten and maize-starch + potatoes.

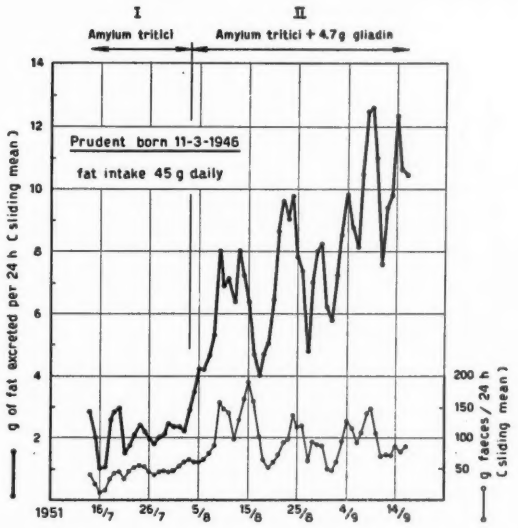

Fig. 3. Excretion of fat in the faeces when on diets containing respectively, amylum tritici and amylum tritici + gliadin.

100 ml water, in which 15—20 g rice flour or wheat starch were cooked and 10—20 g glucose; one meal consisting of 50—100 g potatoes and 75—150 g vegetables (stewed apples, carrots, spinach, endive, Belgian endive or beet root), bouillon from lean meat as gravy. Some children were also given 10—15 g lean meat. For the rest, 50 ml orange juice or 100 ml tomato juice, 100 mg vit. C, 2000—2500 I.U. vit. A and 2000—2500 I.U. vit D.

The daily fat excretion of two patients is plotted in the figures 3—7.

The patient, Prudent (♂, born 11.3. 1946) had already been 2 years in the Wilhelmina Children's Hospital in Utrecht; he had a typical coeliac history, complained with all criteria necessary to diagnose idiopathic coeliac disease and was sensitive to wheat. Height at the beginning of the trial period 103 cm, weight 14.6 kg.

The patient, Maryan (♀, born 24.6. 1944), had been 6 months in the Wilhelmina Children's Hospital in Utrecht; the history showed a slight coeliac disease, she complained with all criteria for diagnosing idiopathic coeliac disease in a mild form. Sensitive to wheat, less so, however than Prudent. Height at the beginning of the trial period 112 cm, weight 18 kg.

The patient, Toos (♀, born 8.9. 1946) had been 3 months in the Wilhelmina Children's Hospital in Utrecht, typical coeliac history, complained with all criteria for diagnosing idiopathic coeliac disease. Sensitive to wheat, less so than Prudent, but more than Maryan. Height at the beginning of the trial period 88 cm, weight 12.4 kg.

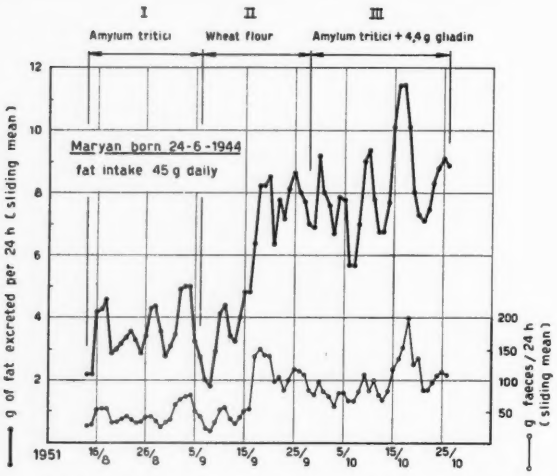

Fig. 4. Excretion of fat in the faeces when on diets containing respectively, amylum tritici, wheat-flour and amylum tritici + gliadin.

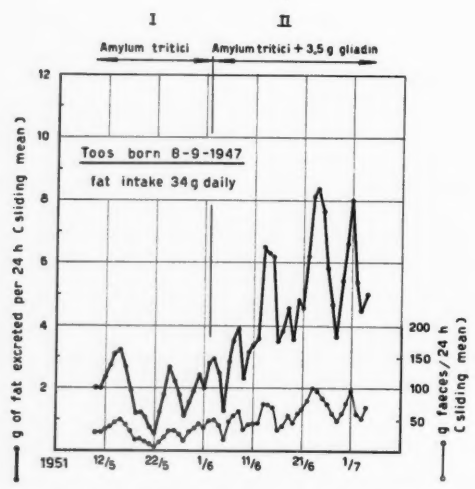

Fig. 5. Excretion of fat in the faeces when on diets containing respectively, amylum tritici and amylum tritici + gliadin.

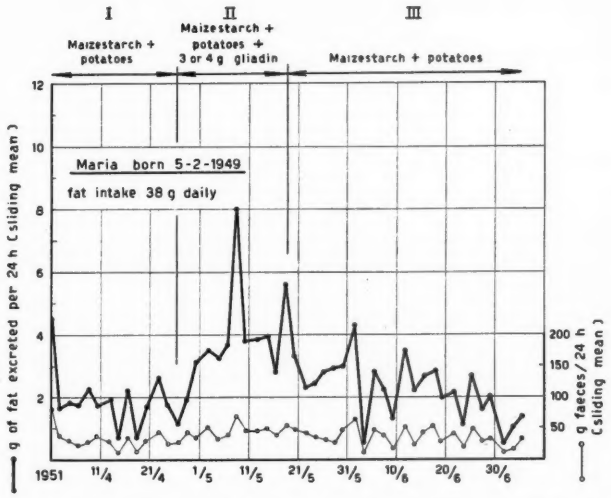

Fig. 6. Excretion of fat in the faeces when on diets containing respectively, maize-starch + potatoes, maize-starch + potatoes + gliadin and maize-starch + potatoes.

The diet of the two following patients (Maria and Jan) consisted of: 750—950 ml cow's milk, 10—15 g sugar, 38—76 g glucose, 100—125 g vegetables (carrots, stewed apples or endive), 1 egg or 60 g lean meat, 15—20 g butterfat, 100—125 g apple juice, 100—150 g apple, 70—100 g starch in the form of potatoes, maize starch or oat meal.

During the whole trial period, Maria, daily took in addition a tablet consisting of: thiamin 5 mg, riboflavin 2 mg, nicotinamide 20 mg, calcium pantothenate 3 mg, adermine HCl 2 mg, ferro sulphate 50 mg, Saccharomyces cerevisiae 150 mg and Extractum hepatici siccum 100 mg.

The patient, Maria (♀, born 5.2. 1949) had been in the Juliana Children's Hospital in The Hague for 6 months; she had a typical coeliac history and was sensitive to wheat. Height at the beginning of the trial period 80 cm, weight 11.5 kg.

The patient, Jan (♂, born 20.7. 1941) had been 3 months in the Juliana Children's Hospital in The Hague; sensitive to wheat. Height at the beginning of the trial period 117 cm, weight 22.1 kg.

From the above figures it follows that gliadin — as well as gluten — causes considerable steatorrhoea, in the same degree as had been previously established on administration of wheat flour (5). From fig. 7 it follows, moreover, that in this patient oat meal also has a harmful effect.

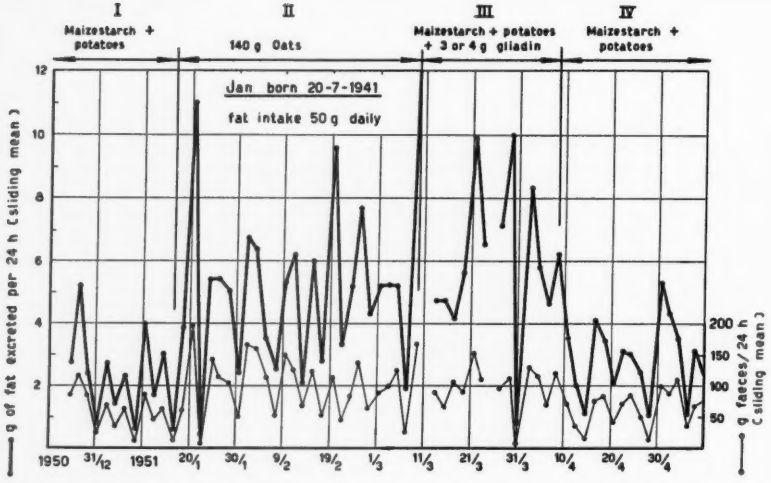

Fig. 7. Excretion of fat in the faeces when on diets containing respectively, maize starch + potatoes, oats, maize-starch + potatoes + gliadin and maize-starch + potatoes.

Clinically, the reaction was exactly the same as that of wheat flour. Thus these results confirm the observations made in the case of the patient Mechie.

This investigation brings us to the conclusion that the injurious action of wheat must be sought principally in the gliadin fraction.

Addendum

During the course of these investigations FRAZER et al. came to the same conclusions concerning the harmful influence of wheat gluten (2, 3).

Summary

Based on the results of an investigation of a number of patients with coeliac disease, the harmful action of wheat flour was shown to be chiefly inherent to the gliadin fraction.

Maladie coeliaque. IV. Étude des constituants néfastes du blé en rapport avec son action sur des malades atteints de maladie coeliaque.

Ce travail repose sur une étude d'un certain nombre de malades atteints de maladie coeliaque. Il est montré que l'action nuisible de la farine de blé est due principalement à la fraction gliadine.

Coeliakie: IV. Untersuchungen über die gefährlichen Bestandteile des Weizens in Zusammenhang mit ihrem Einfluss auf Patienten mit Coeliakie.

Basierend auf den Untersuchungsergebnissen bei einer Anzahl von Patienten mit Coeliakie wird gezeigt, dass der schädliche Einfluss von Weizenmehl hauptsächlich an die Gliadin-Fraktion gebunden ist.

Enfermedad celíaca. IV. Investigación sobre el componente perjudicial del trigo en relación con su acción en pacientes con enfermedad celíaca.

Basados en los resultados realizados en un número de pacientes con enfermedad celíaca se ha demostrado que la acción perjudicial de la harina de trigo era debida especialmente a la fracción gliadina.

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Central Institute for
Nutrition Research T.N.O.
Utrecht. The Netherlands.

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Kinderabteilung des staatlichen Krankenhauses in Most — Vorstand Prim. MUDr. J. Dvořák, Parasitologisches Institut der Karls-Universität in Praha — Vorstand Prof. Dr O. Jírovec, Tschechoslowakei.

Diagnostik und Therapie der durch Pneumocystis carinii verursachten parasitären atypischen Pneumonien bei Säuglingen

von JINDŘICH DVOŘÁK und OTTO JÍROVEC

Der Pathologe Vaněk und Parasitologe Jírovec (Vaněk-Jírovec (1951, 1952)) haben das Protozoon *Pneumocystis carinii* als pathogenes Agens der grösstenteils tödlich verlaufenden, sogenannten interstitiellen Plasmazellenpneumonien speziell der frühgeborenen oder durch Krankheit erschöpften Säuglinge nachgewiesen.

Die Kinderärzte haben schon früher das klinische Bild der sogenannten interstitiellen Plasmazellenpneumonien gekannt, aber die Ätiologie blieb ihnen unbekannt. Es wurde angenommen dass diese Pneumonien als eine spezielle Reaktion des noch unreifen Lungenparenchyms der Säuglinge infolge bakterieller oder eher Virus-Infektion entstanden sind. Andererseits war auch das Protozoon *Pneumocystis carinii* schon lange als Parasit der Lungen verschiedener kleiner Laboratoriumstiere bekannt (Mäuse, Ratten, Meeresschweinchen, Hund u. a.). Chagas fand diesen Parasiten auch beim Menschen im Falle einer Trypanosoma cruzi-Infektion in Brasilien bereits im Jahre 1911. 30 Jahre später beschrieben van der Meer und Brug (1942) bei einem 3 Monate alten an kongenitalem Herzfehler gestorbenen Kinde aus Holland den gleichen Parasiten in der Lunge in Form von Schaumsubstanz, in der 1- bis 8-kernige kleine Pneumocystisparasiten gelagert waren. Eine histopathologische Beschreibung gaben sie aber nicht und der Zusammenhang mit der damals bereits bekannten atypischen interstitiellen Pneumonie blieb von ihnen unerkannt. Bei einem anderen 4-Monate alten Kinde und einem 21-jährigen Manne, die beide aus anderen gründen starben, fanden sie je ein Pneumocystis-Stadium.

Vaněk-Jírovec (1952) untersuchten 16 an atypischer Pneumonie gestorbene Kinder im Alter vom 2—4 Monaten, die grösstenteils frühgeboren oder durch interkurrente Krankheiten geschwächt waren. Die Krankheit selbst dauerte durchschnittlich 9 Tage (4—13), verlief ohne Fieber oder mit leicht erhöhter Temperatur. In ihrem Verlaufe entwickelte sich progressive Tachypnoë und schwere Zyanose. Physikalische Befunde an den Lungen waren nur wenig ausgeprägt. Im Roentgenbild waren nur mehr oder minder ausgebreitete Lungenverschattungen, die sich im Laufe der Krankheit vergrösserten. Die Sektion zeigte feste, schwere Lungen, mit glatter Pleura. In ihrem ventralen Teile war vesikuläres, manchmal interstitielles Emphysem. Die sonst glatte, graue Schnittfläche zeigte charakteristische, durch Verdickung der interlobulären Septen bedingte Struktur. Als Todesursache konnte in allen 16 Fällen eindeutig Pneumonie festgestellt werden. Histopathologische Untersuchung zeigte ein verdicktes

und durch Plasmazellen und Lymphocyten infiltriertes Interstitium. Die Alveolen waren von schaumartigen, aus Parasiten bestehenden Massen ausgefüllt. Die Parasiten selbst bestehen aus einer Schleimkugel von 5—10 μ Durchmesser, in deren Inneren einkernige, 2—4 μ lange, unregelmässige oder rundliche bis längliche Parasitenkörper gelagert sind. Diese Parasiten vermehren sich durch Zweiteilung, immer von den Schleimkugeln umgeben. Ausser dieser Zweiteilung kommt es noch zu einer sporogonialen Vermehrung in 8 sporenartige Gebilde von 2 × 1 μ, wodurch der Entwicklungszyklus offenbar zu Ende ist. Beide Autoren nehmen an, dass die Infektion der Säuglinge entweder per os durch mit Pneumocystis-Sporen verunreinigte Nahrung oder durch Inhalation von Pneumocystis-Sporen in Speicheltröpfchen oder Sputumpartikeln von latent infizierten Erwachsenen geschehen kann. Zur Therapie empfahlen sie protozoocide Heilmittel wie Atebrin, Plasmochin, Paludrin, Chinin, Salvarsan, Fuadin u. a.

Im Laufe des Jahres 1951/52 konnten dann in der Tschechoslowakei weitere 56 Pneumocystis-Pneumonien aufgefunden werden und zwar aus verschiedensten Städten Böhmens und Mährens, so dass bis jetzt aus der Tschechoslowakei 74 Pneumocystis-Fälle bekannt sind. Bei Erwachsenen wurde bis jetzt Pneumocystis nur einmal von VANĚK als Nebenbefund bei einer 60-jährigen an Lymphogranuloma malign. gestorbenen Frau beobachtet. Von den 73 Kinder-Fällen endeten 63 tödlich, 8 konnten durch Wirkung protozoocider Arzheimittel wie Atebrin, Plasmochin, Chinin und Arsaphen (= Stovarsol) gerettet werden. 2 weitere genasen spontan. Offenbar handelt es sich um eine weit verbreitete Säuglingskrankheit, die wir nunmehr auch erfolgreich therapeutisch behandeln können.

In dieser Mitteilung berichten wir über 7 Pneumocystis-Fälle die im Jahre 1951/52 in der Kinderabteilung des Krankenhauses zu Most (ČSR) beobachtet wurden.

In der Zeit von Anfang 1951 bis Juli 1952 starben in der Kinderabteilung Most 4 Kinder mit folgenden klinischen Zeichen: schwere Cyanose, Tachypnoë (Atmungsfrequenz: 90—120 pro Minute), leicht erhöhte Temperatur (bis zu 38° C) und vergrösserte Leber und Milz. An den Lungen war der physikalische Befund im Vergleich zu dem roentgenologischen sehr arm: höchstens leichte bronchiale Atmung mit Rasselgeräuschen über den Lungen. Das Röntgenbild zeigte bandartige Verschattung wie bei den s. g. interstitiellen Bronchopneumonien. Negativer Ausfall der Kälteagglutination im Blute, sowie der Reaktion nach Paul-Bunnel und der serologischen Reaktion auf Grippenantikörper. Das Blutbild war nicht charakteristisch, das rote Blutbild kaum wesentlich verändert, Leukocyten 9 800—24 200, Eosinophilie 0,8—8 %, leichte Linksverschiebung (bis zu 17 % stabkernige Leukocyten). Bei 2 Kindern war das pathologische Bild so schwer, dass es bei einem zum subkutanen und mediastinalen Emphysem und beim anderen zum spontanen Pneumothorax kam. Die Tuberkulinproben und WaR waren bei allen Kindern negativ, die Senkungsgeschwindigkeit der Erytrocyten nach Westergren nur leicht erhöht. Behandlung mit Penicillin (2 × täglich 100 000 Einh. i. m.), Dihydrostreptomycin (4 × täglich 100 mg i. m.), Aureomycin (4 × 60

mg täglich per os), oder Chloromycetin anstatt Aureomycin (4 × 60 mg täglich per os) war erfolglos. Bei allen 4 Kindern konnte an mit Trichrom gefärbten Schnitten charakteristische interstitielle Pneumonie mit zahlreichen schaumartigen Parasitenmassen in den Alveolen und Bronchiolen nachgewiesen werden (Dr. Alois Šebek — Most).

1. Knabe P.V., geb. 19.5. 1951, Geburtsgewicht 3500 g. Zum erstenmal in unserer Kinderabt. vom 19.7. 1951 bis 31.7. 1951 wegen Intoxicatio alimentaris, Dystrophia und Otitis m. cath. lat. sin. Am 18.8. 1951 vom neuen aufgenommen wegen Phlegmone am Hinterkopf, die sogleich inzidiert wurde. Rtg. der Lunge normal. Mantoux 1:1000 neg. Lumbalpunktion: Pandy plus, Zellzahl: 42/3 Lymphocyten. Therapie Penicillin vom 18.8.—2.9., vom 31.8.—3.9. Chloromycetin und dazu 8 Bluttransfusionen. Am 12.9. wird das Kind sehr unruhig, atmet stossartig und wird schwer zyanotisch. Im Roentgenbild Verschattung des linken unteren Lungenfeldes. Erneut wird Penicillin gegeben, doch das Kind stirbt am 14.9. 1951 unter dem Krankheitsbilde einer starken Zyanose und Tachypnoë. Sektionsbefund: Pneumonia interstitialis parasitaria (*Pneumocystis carinii*) lobos ferre omnes pulmonum occupans in regressione (Abb. 1, 2.)

2. Knabe J. R., geb. 26.6. 1951. Geburtsgewicht 3100 g. Zum erstenmal in unserer Kinderabt. vom 25.8.—23.10. 1951 wegen Intoxicatio alimentaris, Otitis med. pur. bilateralis, Mastoiditis bil., Antrotomia bil., Dystrophia, Meningitis ac. abakter., Abscessus periproctalis. Lungen ohne Rtg. Befund. Am 5.11. 1951 von neuem aufgenommen, da er zu Hause hustete und die letzten 2 Tage schwer atmete und zyanotisch war. Das Kind ist atrophisch, zyanotisch, atmet rasch, die Milz ist tastbar, Leber um 3 Finger unter dem Rippen bogenrand vergrössert. Lungen-Rtg.: paracardial links mittelmässige perihiläre Verschattung. Mantoux 1:1000 neg. Blutbild Er. 5,310.000, Hb. 104 %, F.I. 0,98, L. 9800, Stab. 1 %, Plasm. 1 %, Segm. 57 %, Mono. 3 %, Ly. 38 %. Otitis med. sup. dx. Wir gaben Depôt-Penicillin 300.000 E. täglich und Aureomycin. Da das Kind die gleichen klinischen Zeichen aufwies wie das vorherige, fassten wir Verdacht auf Pneumocystis-Pneumonie und behandelten noch mit Arsaphen (= Arsenpreparat Stovarsol) à 0,01 g As i.m. während 3 Tagen (6, 7, 8, 11.). Doch die Zyanose nahm zu, das Kind atmete rasch und stossartig mit Einziehungen der interkostalen Räume und starb am 10.11. Vorherige Lumbalpunktion und Kälteagglutination waren negativ. Sektionsbefund: Pneumonia interstitialis parasitaria (*Pneumocystis carinii*) lobos omnes pulmonum praeter partes aliquot ventrales occupans. (Abb. 3—5.)

3. Knabe J. P., geb. 10.10. 1951. Geburtsgewicht 2700 g. Das Kind war 14 Tage zu Hause krank und hustete und wurde auf unsere Abteilung am 25.11. 1951 mit der Diagnose Bronchopneumonia bil., Otitis med. sup. lat. sin, cath. dx. aufgenommen. Blutbild Er. 3,990.000, Hb. 85 %, F.I. 1,05, L. 24.800, Stab. 17,6 %, Segm. 17,6 %, Mono. 4,8 %, Ly. 52 %, Metamyelo. 8 %. Lumbalpunktion: Pandy + Zellzahl: 72/3 Lymfo. Behandlung: Penicillin, Aureomycin und Phleboclysma. Nach 14 Tagen verschwindet der pathol. Befund der Lungen sowie des Liquors. 5 Bluttransfusionen und nach Weglassen des Penicillins und Aureomycins wird Chloromycetin eingesetzt. Trotzdem bleiben subfebrile Temperaturen bestehen. Am 34. Tage wird rechtsseitige Antrotomie durchgeführt und nochmals Penicillin, Aureomycin und Amigen 100 cc i.v. pro Tag eingesetzt. Am 40. Tage Rtg. der Lungen, das keine Infiltration mehr zeigt. Penicillin weggelassen, der Zustand offensichtlich gebessert. Vom 51.—58. Tag wieder Chloromycetin, weitere 3 Transfusionen und Amigen-Infusionen. Am 65. Tage ist der Zustand verschlimmert; von neuem Chloromycetin. Am 68. Tage wird das

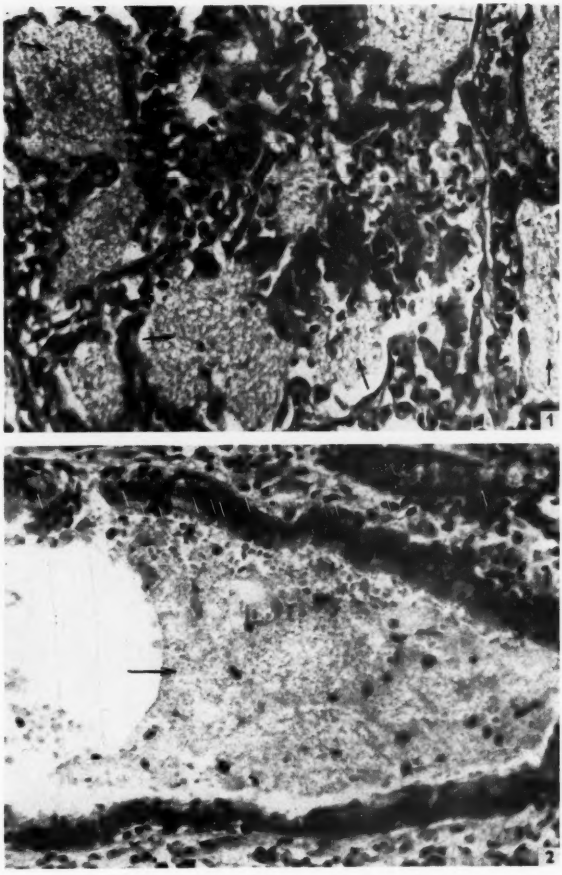
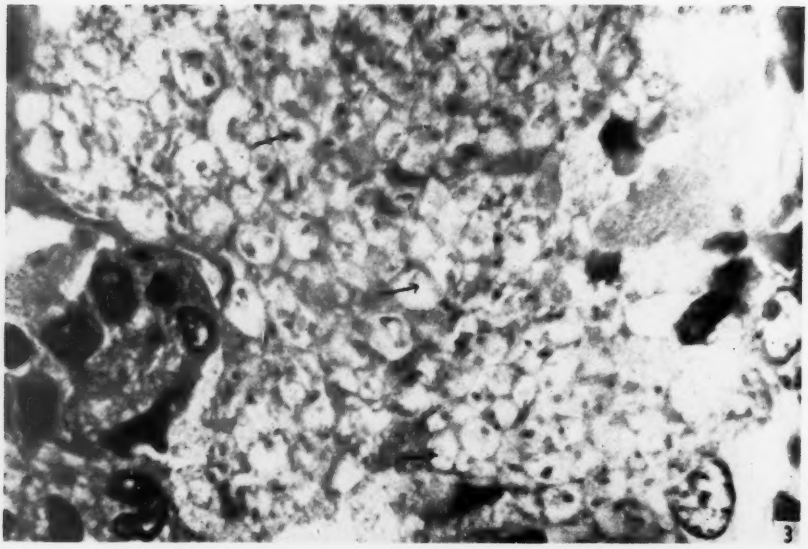
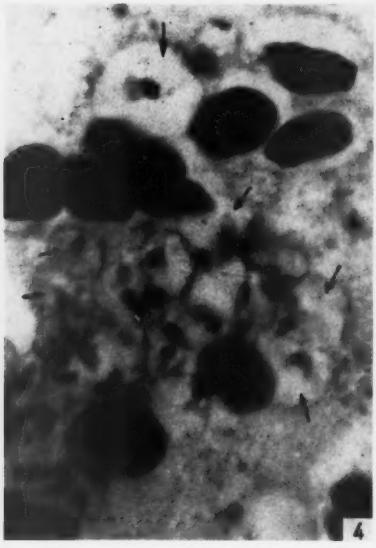


Abb. 1. Schaumartige Pneumocystis-Massen in den Lungen-Alveolen des Patienten Nr. 1. Formol-Trichrom. 200 ×. — Abb. 2. Parasitenmassen in Bronchiolen des Patienten Nr. 1. Formol-Trichrom. 100 ×.

Kind zyanotisch, atmet erschwert, mit Einziehungen der interkostalen Räume. Blutbild Er. 4,890.000, Hb. 80 %, F.I. 0,82, L. 15,000, Ly. 57,6 %, Seg. 28 %, Eo. 3.2 %, Stab. 7.2 %, Mono. 3,2 %, Plasma. 0,8 %. Statt Chloromycetin wird Aureomycin gegeben und am 69. Tage 2 × 200.000 E. Penicillin. Röntgenbild Abb. 6. Am 71. Tage hochgradige Zyanose: Atem-Frequenz 114 pro Min., am 72. Tage 126 und am 73. Tage 123 pro Min. Erst jetzt wurde Plasmochin 5 × 0,001 eingesetzt, doch das sehr herunter gekommene Kind stirbt am gleichen Tage. Sektionsbefund: Pneumonia parasitaria (*Pneumocystis carinii*). Dieser Fall zeigt eindeutig die Unwirksamkeit der Antibiotica bei dieser Art von Pneumonie. Plasmochin wurde zu spät eingesetzt.





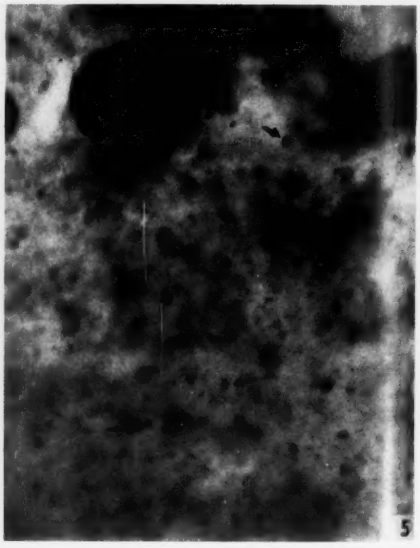


Abb. 3. *Pneumocystis carinii* im Lungenschnitt (Patient Nr. 2) bei starker Vergrösse ng. Einzelne, in den Schleimkugeln gelagerte Parasiten gut sichtbar. Formol-Trichrom. 10 ×. — Abb. 4. Feucht fixierter Ausstrich aus den Lungen des Patienten Nr. 2. Schleimk geln gut erhalten, in ihnen liegen die Parasiten. Sublimat-Alkohol, Trichrom. 1 500 ×. — Al . 5. Trockenausstrich aus den Lungen des Patienten Nr. 2. Die Schleimkugeln geschru pft, die Parasiten als dunkle Punkte sichtbar. Methylalkohol, Giemsa. 800 ×.

(Alle Mikrophotographien von O. Jíro ec.)

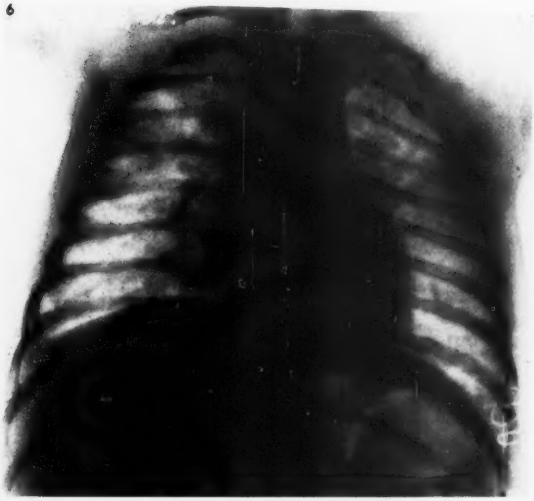


Abb. 6. Röntgenbild des Patienten Nr. 3 (J. P.) am 4/11. 1952.

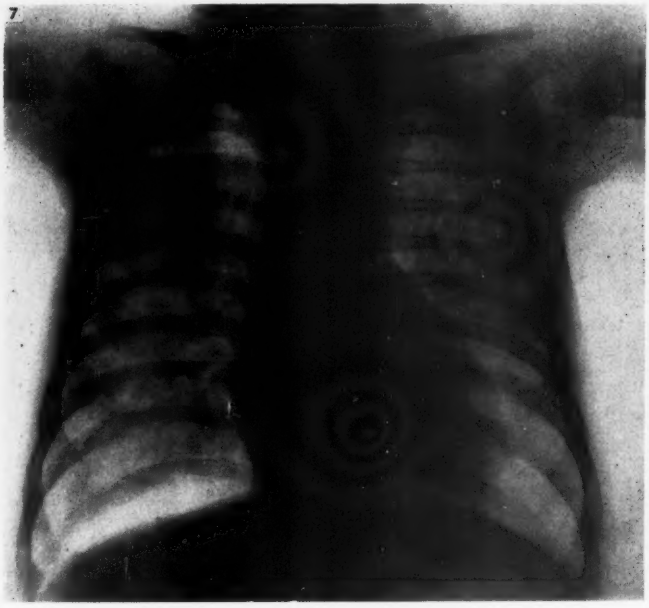


Abb. 7. Röntgenbild des Patienten Nr. 4 (A. R.), durch Sektion als Pneumocystis-Pneumonie bestätigt. Beiderseitige Bronchopneumonie aus welcher rechtsseitiger spontaner Pneumothorax entstanden ist. 24/5. 1952.

Abb. 8. Röntgenbild des Patienten Nr. 5. (J. P.) Die durch Pneumocystis verursachten Lungenveränderungen im Parenchym beider Teile sind so weitgehend, dass es zum mediastinalen und subkutanen Emphysem kam. Der Patient konnte durch Atebrin-Plasmochin gerettet werden.

4. Knabe A. R., geb. 21.1. 1952. Aufgenommen 24/5 in schlechtem Zustande, zyanotisch, Tachypnoë 100—110 Atemzüge pro Min. Beiderseitige Pneumonie und spontaner Pneumothorax rechts. Röntgenbild Abb. 7. Zu Hause ohne Fieber, bei uns 38°–38°,8 C. Blutbild Er. 5,230.000, Hb. 100 %, F.I. 0,96, L. 18.400, Eo. 0,8 %, Stab. 1,6 %, Plasmaz. 0,8 %, Segm. 57,6 %, Mono. 2,4 %, Lym. 36,8 %. Tuberkulin neg. Das Kind bekam Penicillin, Aureomycin, Sauerstoff und Analeptika. Die Zyanose und Tachypnoë bezogen wir auf die beiderseitige Pneumonie und den Pneumothorax. Antibiotica-Behandlung hatte aber keinen Erfolg und das Kind starb am 28.5. Sektionsbefund: Pneumonia parasitaria bilateralis (*Pneumocystis carinii*), spontaner Pneumothorax rechts.

Ausser diesen 4 leider verstorbenen Kindern, bei denen durch Sektion die Diagnose Pneumocystis-Pneumonie eindeutig festgestellt werden konnte, gelang es uns weitere 3 Kinder, bei denen alle klinischen Zeichen uns auch zur Diagnose Pneumocystis-Pneumonie führten, mit Hilfe von Plasmochin und Atebrin zu retten.

5. Knabe J. P., geb. 22.4. 1951. Geburtsgewicht 2500 g, zum erstenmal in unserer Kinderabteilung vom 14.9. wegen Intoxicatio alimentaris, Bronchopneumonia lat. dx. Am 12.11. 1951 von neuem in unsere Abteilung aufgenommen, da er seit 2 Tagen schwer atmete und zyanotisch wurde. Bei der Aufnahme war das Kind bewusstlos, zyanotisch, mit Einziehungen der interkostalen Räume. Lungen-Rtg.: im rechten Lungenfeld 2 bandartige Schatten von interstitiellem Charakter (Abb. 8). Mantoux 1:1000 neg. Blutbild 4,728.000, Hb. 79 %, L. 13000, Stab. 4 %, Segm. 19 %, Mono.

3 %, Lym. 74 %. Kälteagglutination, ebenso wie Vidal, Paul-Bunnel-Reaktion und WaR. waren neg. Lumbalpunktion auch neg.; BSR nach Westergren 8/21 mm. Haemagglutination-Inhibitionstest auf Grippenantikörper negativ. Blutspektrum zeigte Absorbtion in 578—588 μμ und 540—555 μμ, was für Oxyhaemoglobin und nicht für Methaemoglobin sprechen würde. Trotz Anwendung von Antibiotica verschlimmerte sich die Tachypnoë, die Zyanose und das Rtg.-Bild. Am 13. Tage der jetzigen Erkrankung entwickelte sich ein Unterhautemphysem am ganzen Rumpfe, später mediastinales Emphysem, welches erst am 21. Tage verschwand. Da die klinischen Zeichen die gleichen wie in allen vorher beschriebenen Fällen waren und auch die Antibiotica total versagten, stellten wir die klinische Diagnose: Pneumocystis-Pneumonie und setzten die Behandlung mit Atebrin (2 × 0,025 g täglich) während 7 Tagen und dann Plasmochin (5 × 0,001 g täglich) während 6 Tagen (siehe Tab. 1). Das Kind genas trotz interkurrenter Varicellen und ist jetzt vollkommen gesund.

6. Knabe J.Š., geb. am 13.11. 1951, Geburtsgewicht 2300 g. Überwiesen aus Geburtsanstalt in Most am 21.11. 1951 wegen Intoxicatio alimentaris, Partus praematurus, Meningitis ac. abakt., Pleuritis mediastinalis dx. Das Kind wollte 2 Tage nicht trinken, war sehr müde ohne spontane Bewegungen. Durch Penicillin konnte der Zustand weitgehend gebessert werden und das Kind wurde nach Hause entlassen. Am 25.1. 1952 wurde das Kind wieder in unsere Abteilung aufgenommen. Seit 2 Tagen erhöhte Temperatur, Zyanose, stossartige, beschleunigte Atmung. Über den Lungen gedämpfte Perkussion mit leichter Bronchialatmung und einzelnen Rasselgeräuschen. Die Leber 8 cm unter dem Rippenbogen. Die Milz hart, reicht bis 5 cm unter den Rippenbogen. Lungen-Rtg.: beiderseitige Pneumonie mit einer stärkeren Verschattung links. Mantoux 1:1000 neg. Blutbild: Er. 4,950.000, Hb. 87 %, F.I. 0,88, L. 24.000, Eo. 1 %, Stab. 13 %, Plasmaz. 1 %, Segm. 57,5 %, Mono. 4,5 %, Lym. 23 %, Normoblasten 2,5 %, Anisocytose. Trombocyten 214.000, Blutgerinnung: 3 Min., Blutungszeit: 1 Min. 10 Sekunden. Kälteagglutination im Blute negativ. Furunkulose und Phlegmone am Hinterkopf, Otitis med. cath. dx. — Infolge der beobachteten klinischen Zeichen wird die Diagnose Pneumocystis-Pneumonie gestellt, und zu ihrer Erhärterung verordneten wir zuerst Penicillin, Aureomycin und Sauerstoff-Zelt. Das Kind hat ständig 80—90 Atemzüge pro Minute, physikalischer Lungen befund arm, Zyanose unverändert. Deshalb werden am 7. Tage die Antibiotica fortgelassen und zuerst Plasmochin 5 × 0,001 und später Atebrin 2 × 0,025 g täglich eingesetzt. Am 9. Tage weicht die Zyanose, um am 12. Tage vollständig zu verschwinden. Atmungsfrequenz beträgt 72 pro Minute. Am 14. Tage wird Plasmochin weggelassen, Atmungsfrequenz 54 pro Minute. Der Zustand augenscheinlich gebessert. Im Röntgenbild: beiderseitige, parahilär leicht verminderte Transparenz. Am 15. Tage bildet sich am Hinterkopf eine Phlegmone, deshalb wird nochmals Penicillin und Streptomycin i.m., sowie Atebrin 2 × 0,025 per os zur Sicherung des protozoociden Effektes des Plasmochins appliziert. Atmungsfrequenz 54 pro Minute. Am 18. Tage weitere Regression des Roentgenbefundes. Leber und Milz tastbar, Atmungsfrequenz 54 pro Minute. Erste Transfusion gegeben. Das Kind genas. (Siehe Tabelle Nr. 2.)

7. Knabe K. T., geb. 1.1. 1952, Geburtsgewicht 3100 g. Am 31.1. 1952 in unsere Abteilung aufgenommen wegen Tachypnoë, Zyanose und beiderseitige Pneumonie. Vor 10 Tagen Husten und Temperaturerhöhung bis zu 38° C. Das Kind magert ab, erbricht und wird dystrophisch. Wir gaben Penicillin, Aureomycin, ferner Analeptica, Senfpflaster und Sauerstoffzelt. Die Milz war tastbar, die Leber um 2 Finger vergrössert. Die Tachypnoë und Zyanose dauert an, deshalb wird am 4.4. zusätzlich noch Plasmochin 5 × 0,001 g pro Tag während 6 Tagen gegeben. Am 10.4. ist der Zustand

TABELLE 1

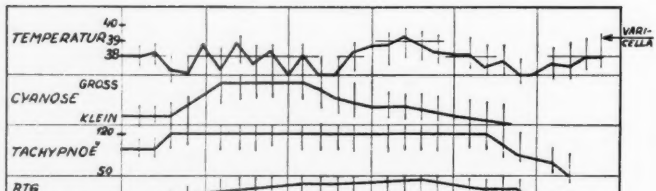
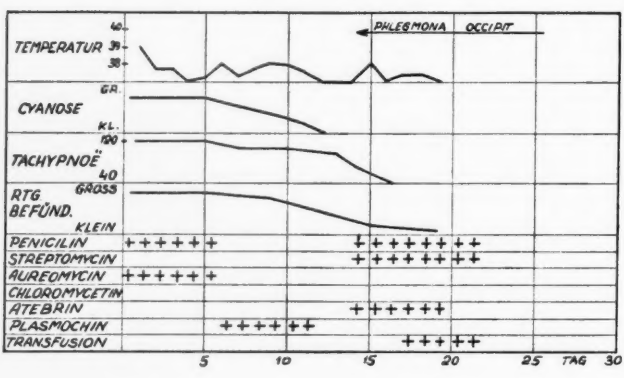


TABELLE 2



des Kindes deutlich gebessert, die Zyanose ist verschwunden. Penicillin wird weggelassen. Seit dem 17.4. werden 4 Bluttransfusionen gegeben und zusätzlich noch Streptomycin 4 × 100 mg täglich. Am 26.4. werden Penicillin und Streptomycin weggelassen und während weiterer 5 Tage Atebrin 4 × 0,01 g pro Tag gegeben. Der Zustand hat sich endgültig gebessert und am 26.4. zeigt das Roentgenbild ein fast totales Verschwinden der Infiltration. Wegen Mastoiditis musste beiderseitige Antrotomie durchgeführt werden, welche vom Kinde ganz gut vertragen wurde. Das Kind ist gesund bis zum heutigen Tage.

Diskussion

Unsere Erfahrungen an 7 Pneumocystis-Pneumonien, von denen 4 durch Sektion als solche mit Sicherheit erkannt wurden, zeugen dafür, dass an diese Krankheit immer in solchen Fällen gedacht werden muss, wenn es sich um frühgeborene, dystrophische oder künstlich ernährte Kinder handelt, die an Pneumonie mit starker Zyanose und Tachypnoë (90—120 Atemzüge pro Minute) erkrankt sind und bei denen die Behandlung mit Antibiotika, besonders mit Aureomycin und Chloromycetin, erfolglos ist. In solchen Fällen geben wir gleichzeitig mit den Antibiotika noch Plasmochin während 6 Tagen 5×1—2 mg täglich und nachher Atebrin 4—$5 \times 0{,}01$ g während 6 Tagen. Weitere Erfahrungen müssen zeigen, ob auch andere Antimalarika wie z. B. Paludrin, Chlorochin u. a. wirksam sind. Wir empfehlen diese Heilmittel genügend lange Zeit anzuwenden, da die pathologischen Veränderungen an den Lungen sehr bedeutend sind und erst langsam weichen.

Was die Diagnose anbetrifft sind wir am lebenden Kinde vorläufig nur auf die oben erwähnten klinischen Symptome angewiesen, die aber sehr charakteristisch sind und bei gewisser Erfahrung jedenfalls genügen, die Diagnose *Pneumocystis-Pneumonie* zu stellen. Differential-diagnostisch von Bedeutung ist auch die Wirkungslosigkeit der Antibiotica besonders des Aureomycins und Chloromycetins, welche sonst bei folgenden Pneumonien gut wirksam sind: a) bei bakteriellen Pneumonien, b) bei Virus-Pneumonien, das ist bei primären atypischen Pneumonien und bei anderen aus der Virus-Gruppe Eaton, dann bei der Psittakose, c) bei den Rickettsiosen, Q-Fieber und anderen. Primäre atypische Pneumonien werden auf Grund negativer Kälte-Agglutination unwahrscheinlich. Grippepneumonien, die auch auf Aureomycin und Chloromycetin schlecht reagieren, werden auf Grund des negativen Nachweises von Grippeantikörpern im Blute ausgeschlossen. Pneumonien bei der Mononucleose werden durch die positive Paul-Bunnel-Reaktion diagnostiziert. An Schnitten durch verschiedene Organe der verstorbenen Kinder konnten wir keine Toxoplasmen entdecken. Wir sind uns bewusst, dass bei den geheilten Kindern ein eindeutiger Beweis für die Pneumocystis-Pneumonie nicht gegeben werden kann, solange uns spezifische serologische oder imunobiologische Reaktionen fehlen. Die einzige exakte Diagnose kann erst bei der Sektion gemacht werden. Bis jetzt haben wir vergeblich nach verschiedenen Entwicklungsstadien von Pneumocystis in Mund, Nase und Rachen der infizierten Säuglinge gesucht. Bei der Fragilität der Schleimkugel-Stadien und bei der Kleinheit der Sporen von Pneumocystis und — falls sie isoliert wären — wegen ihrer Ähnlichkeit mit grösseren Kokken ist solches Suchen fast aussichtslos.

Differentialdiagnostisch kommen neben den oben genannten Pneumonie-arten noch die lipoide Pneumonie, Löfflers eosinophile Pneumonie, Aspirationspneumonie und Atelektase in Betracht, welche aber anamnestisch, epidemiologisch und klinisch ausgeschlossen werden können.

Wir versuchten auch intrakutane Teste mit einem Antigen hergestellt, aus infizierten Lungen, welche möglichst frisch entnommen, fein zerkleinert und während 24—48 Stunden bei 37° C getrocknet wurden. Nachher wurden sie pulverisiert und 1 g davon während 4—8 Tagen bei 37° C in 100 ccm 0,8 % NaCl plus 0,5 % Phenol extrahiert. Nach Filtrieren und Sterilitätsprüfung füllten wir das Antigen in Ampullen. Wir injizierten intradermal 0,05—0,1 cc Antigen und als Kontrolle die gleiche Menge von 0,5 Phenol-NaCl. Die Ablesung erfolgte nach 30 Minuten, dann nach 6, 12, 24, und 48 Stunden. Das Resultat war bis jetzt an 10 Säuglingen negativ. Auch bei 11 erwachsenen Pflegerinnen der Kinderabteilung in Most war die intrakutane Reaktion mit 3 verschiedenen Antigenproben negativ zu bewerten. Bei einigen erschien zwar innerhalb 30 Minuten ein etwa 20 × 30 mm grosses leichtes Erythem, das aber bereits nach 4 Stunden verschwunden war. Bei keiner der Untersuchten kam es zur Spätreaktion. Die Ursache des negativen Ausfalles der Intrakutanreaktion kann natürlich sehr verschieden sein. Erstens könnten im Antigen die spezifischen Stoffe durch ungeeignete Extraktion oder schon durch das Trocknen zerstört werden. Zweitens ist nur wenig wahrscheinlich, dass Kinder in diesem Alter bei relativ kurz andauernder Infektion schon fähig zur Sensibilisierung gegen die Parasitenantigene wären. Bei Erwachsenen sind wir dann ganz unsicher, ob wirklich eine latente Infektion vorliegt oder nicht. Weitere immunobiologische Untersuchungen sind nötig. Es sei uns gestattet hier noch kurz über unsere Versuche zu berichten, die die Frage klären sollten, ob durch die Parasiten Toxine gebildet werden. Wir injizierten die oben angeführten Antigen Mäusen intravenös und intraperitoneal (0,05—0,1 cc resp. 0,5 cc). Nach Überwinden des durch Phenol verursachten schockartigen Zitterns erholten sich alle Versuchsmäuse und blieben gesund. Zum Vergleich führen wir die Versuche von WEINMAN und KLATCHKO an, die bei Toxoplasmose im Peritonealexudat der infizierten Mäuse ein starkes Toxin nachweisen konnten, das ziemlich thermostabil war und intravenös injiziert (0,1 cc) die Mäuse innerhalb sehr kurzer Zeit tötete.

Die Epidemiologie der Pneumocystis-Pneumonien bleibt z. Z. noch ganz unklar. Fünf der hier beschriebenen Kinder lagen zuerst auf unserer Abteilung wegen anderer Erkrankungen, 4 kehrten nach Hause zurück und wurden nach 10—30 Tagen wieder mit typischen klinischen Zeichen der Pneumocystis-Pneumonie aufgekommen. Ein Kind lag dauernd seit seiner Geburt in der Abteilung und kam überhaupt nicht in ein anderes Milieu. 2 Kinder kamen von aussen bereits mit den typischen Zeichen (Nr. 4 und Nr. 7). Es handelte sich überall um dystrophische bis atrophische Kinder, welche noch durch andere Krankheiten geschwächt waren und die entweder im gleichen Raume oder im Nebenraume lagen. Auch von anderen Stellen berichteten unsere Kollegen, dass Pneumocystis auch bei solchen Kindern vorgekommen ist, die niemals die Kinderabteilungen verlassen haben. An anderer Stelle haben wir angegeben (VANĚK-JÍROVEC), dass folgende Infektionswege möglich sind.

1. Infektion durch Nahrung, welche mit Pneumocystis-Sporen verunreinigt wurde. Als Träger der Infektion kommen in Betracht Mäuse, Ratten, und ev. andere Nage- und Haustiere, die in anderen Ländern (Brasilien, Holland, Frankreich, England u. a.) als infiziert gefunden wurden. Dazu kommt noch die mögliche Verbreitung der Sporen durch Schaben (*Blatta orientalis*, *Blattella germanica*), die in den Krankenhäusern oft vorkommen.

2. Infektion durch Inhalation, sei es durch die in Luft aufgewirbelten Pneumocystis-Sporen, sei es durch Tröpfcheninfektion von Seiten der Eltern oder des Pflegepersonals, da wie aus den Untersuchungen von VAN DER MEER und BRUG sowie VANĚK hervorgeht — auch bei Erwachsenen latente Infektionen möglich sind. Weitere Untersuchungen müssen entscheiden, ob es sich um Nosokomial-Infektionen handelt.

Zusammenfassung

1. Es werden 7 Fälle der durch *Pneumocystis carinii* verursachten Pneumonie bei Säuglingen beschrieben, von denen 4 durch Sektionsbefund als solche histo-parasitologisch diagnostiziert wurden.

2. Drei Fälle konnten durch Plasmochin und Atebrin gerettet werden. Beide Mittel müssen genügend lange gegeben werden, denn die Reparation der befallenen Lunge geschieht nur langsam.

3. Als Grundlage der klinischen Diagnose bei den atypischen parasitären Säuglingspneumonien kann vorläufig folgende TRIAS gelten: a. Zyanose, b. Tachypnoë (Atmungsfrequenz 90—120 pro Minute), c. Fehlschlagen der Antibiotica, insbesondere von Aureomycin und Chloromycetin.

4. Wir schlagen vor, jede Säuglingspneumonie, welche die oben angeführten klinischen Symptome aufweist, unbedingt gleichzeitig mit Plasmochin und Atebrin zu behandeln.

Diagnostic et traitement des pneumonies atypiques parasitaires chez le nourrisson causées par le Pneumocystis carinii.

On décrit sept cas de pneumonies du nourrisson causées par le Pneumocystis carinii dont quatre on été identifiés par l'examen histo-pathologique après l'autopsie. Trois cas ont pu être sauvés par la « Plasmochin » et l' « Atebrin ». Les deux remèdes doivent être donnés assez longtemps car la réparation du poumon touché ne se fait que lentement. Comme base du diagnostic clinique des pneumonies atypiques parasitaires du nourrisson on peut reconnaître comme valable jusqu'à présent la triade suivante: A. cyanose, B. tachypnée (90—120 respirations par minute), C. incativité des antibiotiques, tout d'abord de l'auréomycine puis de la chloromycétine. En tous cas nous proposons de traiter chaque pneumonie du nourrisson qui présente les symptômes cliniques sous-nommés avec la « Plasmochin » et l' « Atebrin ».

Diagnosis and treatment of atypical pneomonia in infants, caused by Pneumocystis carinii.

Seven cases of pneumonia in infants caused by Pneumocystis carinii are described, four of which had a histo-parasitologic diagnosis at post mortem. Three cases were

saved with "Plasmochin" and "Atebrin". Both remedies must be given for a sufficiently long time as the repair of the sick lung is slow. Atypical parasitic pneumonia in infants can be suspected on the basis of the following trial: a) Cyanosis. b) Tachypnoea (respiratory frequency 90—120 per minute). c) No effect of antibiotics, especially aureomycin and chloromycetin. The authors propose treatment with "Plasmochin" and "Atebrin" in cases of pneumonia in infants, where the abovementioned clinical symptoms are present.

Diagnóstico y terapéutica de la neumonía atípica parasitaria de los lactantes producida por el neumocistis carinii.

Se describen 7 casos de neumonía de los lactantes producida por el Pneumocystis carinii de los cuales 4 fueron encontrados en la autopsia y diagnostizados histo-parasitologicamente. Tres casos pudieron ser salvados con plasmoquina y atebrina. Los dos medios tienen que ser administrados un periodo de tiempo suficientemente largo, ya que la reparación del pulmón afectado solo sucede lentamente. Como base del diagnóstico clínico de las neumonias del lactante atípicas parasitarias puede de momento valer la siguiente tríada: A. Cianosis B. Taquipnea (frecuencia respiratoria de 90-a 120 por minuto). C. Fracaso de los antibióticos, especialmente de la aureomicina y cloromicetina. Nosotros proponemos de tratar sin falta toda neumonía de lactante que muestre los síntomas arriba citados al mismo tiempo con plasmoquina y atebrina.

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Nachtrag bei der Korektur

Bis Ende 1952 konnten wir weitere 86 tötliche Pneumocystis-Fälle bei Kleinkindern aus verschiedenen Orten der Tschekoslowakei unter Mitwirkung von unseren Koll. Paediatern und Pathologen feststellen. Somit sind in den Jahren 1951—1952 aus ČSR etwa 160 Pneumocystosis-Fälle bekannt. HERZBERG u. Mitarb. (1952) beschrieben aus Marburg 9 tötliche Fälle, STOPKA (1952) 8 Fälle aus Rostock. Nach brieflicher Mitteilung fanden neuerdings PIEKARSKI in Bonn 3 Fälle und BRANDSTEIN in Budapest 7 Fälle. Es handelt sich also um eine in Mitteleuropa weit verbreitete Infektionskrankheit, der alle nötige Aufmerksamkeit gewidmet werden muss.

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Parasitol. Institut
Viničná 7, Praha II, und
Staatl. Krankenhaus
Most. Tschechoslowakei

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From the University Children's Clinic, Helsinki (Finland). Chief Professor Arvo Ylppö, M.D., and from the State Serum Institute in Finland. Chief Professor Eero Uroma, M.D.

Aetiological Studies on Infantile Diarrhoea in Finland

by ILARI RANTASALO and NIILO HALLMAN

In recent years the incidence of severe infantile diarrhoea in Finland has been considerably higher than normal, and the disease has carried off yearly hundreds of victims (NEVANLINNA and LOUHIVUORI). It appeared throughout the country, and in any season, but has occurred mainly during the summer months. The aetiology of the disease was unknown.

During many years the elucidation of the aetiology of infantile diarrhoea has been the object of a steadily growing interest throughout the world. In some places bacilli of the SALMONELLA and SHIGELLA groups were found in the majority of the patients, whereas elsewhere the role played by these bacteria was less significant (ref. HINDEN). Recent years have seen an awakening of interest in certain strains of Escherichia coli (ADAM; BRAY; GILES; SANGSTER and SMITH; ØRSKOV) which could be isolated in endemics and epidemics at institutions for child care, and which on the other hand have not been found in healthy children, at least not to any great extent.

With the objective of investigating in what measure Finnish material shows bacilli of the SALMONELLA and SHIGELLA groups on the one hand, and on the other the "dyspepsia" coli just mentioned, we have performed studies at the diarrhoea ward of the Children's Clinic of the University Helsinki. To this hospital particularly severely ill children are brought from all over the country, and not only from the town of Helsinki, because about three fourths of the material being from the provinces.

Material och Method

The material which, as already mentioned, was collected at the Children's Clinic of the Helsinki University, is divided into two parts. During the period 1.7.50—28.2.51 only bacilli belonging to the Salmonella and Shigella groups were sought in the stools of infants affected with diarrhoea. During the second period 1.3.51—29.2.52 an additional search was made for following Escherichia coli strains as well: 0-111, 0-55, 0-44, and 0-26.[1] The first part of the material consisted of 259 infants suffering

[1] The bacteria species and control sera were obtained from Dr. FRITS ØRSKOV at Statens Seruminstitut, Copenhagen. In this connection, we gratefully acknowledge our indebtedness to him.

from diarrhoea, the majority of whom were under one year of age. A small number of the infants were 1 to 2 years old. The second part of the series was made up of babies under one year, who all had diarrhoea. The control group consisted of 68 healthy infants under 6 months old from the Child Welfare Centre who had never shown any signs of diarrhoea.

The rectal swabs were taken immediately on admission. Only in a few cases the taking of specimens was postponed for a day or two. Cultures from the stools were simultaneously made in the majority of cases. — For a nutrient the Drigalski agar was used as well as an enrichment medium containing selenite, and the culture was made immediately at the hospital. The Salmonella and Shigella species were studied by means of the fermentation test and slide agglutination (KAUFFMANN). The E. coli strains were studied first by slide agglutination using rabbit serum prepared with a living strain and thereafter by tube agglutination, using a living strain and a strain killed by boiling.

Results

The 259 cases of the first period of investigation have been grouped in *Table 1* according to their ages. Of 33 infants over one year old two had in their excrements the Salmonella paratyphi B and five Shigella Sonnei. Consequently, about one fifth of the cases were cleared up by means of the investigations. Of the 52 patients from 6 to 12 months old one revealed a paratyphoid and 3 a Sonne-type dysentery. The greater part of the series were under six months of age, a total of 176 cases. Two of them had dysentery of the Sonne type; in no instance were bacilli of the Salmonella group revealed by the search. It is noteworthy that all the Salmonellas found were paratyphi B and all Shigellas S. Sonnei. Taking into consideration all the age groups examined, a positive result was obtained in about 5 per cent of the cases, and of them the majority belonged to the oldest age group which is of no particular significance when discussing infantile diarrhoea.

TABLE 1

The Results of Stool Examinations during the Period July 1st 1950—February 28th 1951.

Age	Number of cases	Salm. parat B.	Other Salm.	Shigella Sonnei	Shigella Flexneri	%
1—2 years..	33	2	–	5	–	21.2
½—1 " ..	52	1	–	3	–	7.7
3—6 months	76	–	–	1	–	1.3
0—3 "	98	–	–	1	–	1.0
	259	3	–	10	–	5.0

TABLE 2

The Results of Stool Examinations during the Period March 1st 1951—February 29th 1952.

Age	Number of cases	Salm. parat. B.	S. typhi murium	Other Salm.	Shig. Sonnei	Shig. Flexneri	DC 111	DC 55	DC 26	DC 44	%
1—2 years..		(3)	–	–	–	(1)	?[1]	?[1]	?[1]	?[1]	
½—1 " ..	74	1	1	–	–	–	2	1	4	4	17.6
3—6 months	80	–	1	–	–	–	5	1	12	4	28.8
0—3 "	116	–	–	–	–	–	7	–	13	8	24.1
	270	1	2	–	–	–	14	2	29	16	23.7

[1] Not examined.

The second part of the series comprising cases which were brought for treatment in the course of one year (Table 2) was classified according to age in the following way: under 3 months old 116, 3 to 6 months 80 and over 6 months old 74 babies. The search failed to reveal any bacteria of the Shigella group in these cases. Micro-organisms belonging to the Salmonella group were encountered in 3 cases, one of them S. paratyphi B and two S. typhi murium. In this connection mention should be made of the circumstance that the diarrhoea cases 1 to 2 years old who were treated simultaneously at the hospital had paratyphoid and one a Flexner dysentery in their stools. There is therefore a pronounced difference as compared to the first part of our series. Shigella Sonnei which had frequently been found previously, failed to appear in any instance during the second period.

So-called dyspepsia coli were found in the second part of the series which, in contrast to the first part, was also studied in this respect, in 61 cases all told, equalling about 23 % of the total number of cases. The relatively highest incidence of positive responses occurred in the patients 3 to 6 months old (Table 2), and the lowest in the age group of 6 to 12 months.

The most frequent was E. coli strain 0-26 (29 cases), the least frequent strain 0-55 (2 cases). If conclusions are drawn on the basis of a comparison of the bacilli of the Shigella and Salmonella groups, of which in fact only a few were found in this latter part of the series, it would appear that the last-mentioned groups produce more often diarrhoea in children who have passed the infant age, whereas so-called dyspepsia coli are more frequent in babies under 6 months of age.

In classifying the diarrhoea cases according to the nature of the disease (Table 3): toxic forms, mild diarrhoea and cases essentially associated with respiratory infections such as bronchitis, pneumonia etc., it is found that E.

TABLE 3

The diarrhoeas divided according to the type of disease.

Type of disease	No. of cases	Salm. parat. B.	S. typh. murium	Other Salm.	Shigella	DC 111	DC 55	DC 44	DC 26	%
Gastroenteritis + Intoxicatio....	36	–	–	–	–	9	–	2	11	61.1
Gastroent. ac.....	152	1	2	–	–	4	1	13	14	23.0
Gastroenteritis + Infectio resp...	82	–	–	–	–	1	1	1	4	8.5
	270	1	2	–	–	14	2	16	29	23.7
Healthy children ..	68	–	–	–	–	–	–	1	–	

coli strains were abundantly encountered in severe cases, i.e. in 22 cases out of 36, or in 61 %. The organism most frequently found in toxic diarrhoea was the E. coli strain 0-26 (11 cases) but it was also fairly abundant in milder cases (14 cases), and was encountered to some extent in patients simultaneously affected with respiratory infections (4 cases). From the point of view of incidence the strain 0-111 was most frequent in toxic cases (9/14). Strain 0-44 was only found twice in severe diarrhoea but was relatively abundant in its milder forms (14 cases). Strain 0-55 was encountered twice, and in neither case was the disease particularly severe. We can draw the conclusion that strain 0-111 seems to be present more often in severe diarrhoea, strain 0-26 is found in both severe and mild forms of the disease, and strain 0-44 is usually seen in mild diarrhoea. In any event, it is indisputable that s.c. dyspepsia coli are as a rule rare in cases simultaneously affected with respiratory infections, which suggests a different aetiology for the disease. The significance of dyspepsia coli in the aetiology of diarrhoea is emphasized by the circumstance that their incidence in our series is markedly higher in severe than in mild forms of the disease.

On Table 4 we have moreover grouped the cases according to the season. There does not seem to be any marked accumulation of the E. coli strains under discussion during any particular season.

As already mentioned, the patients included into this series came to the hospital from different parts of Finland. On examining the districts and the times of admission to hospital of the patients one cannot speak of any local epidemic at least on the basis of this material. The only exception is constituted by an orphanage which, at the turn of the year 1951—1952, sent 8 severe cases of diarrhoea, 6 of whom revealed the strain 0-111 in their excrements. On examining the other children at this orphanage, it was found that one

TABLE 4

The cases of diarrhoea divided according to different seasons of the year.

Time	No. of cases	Salm. parat. B	S. typhi murium	Shigella	DC 111	DC 55	DC 44	DC 26
January–March.....	59	–	1	–	1	–	6	7
April–June.....	75	–	–	–	1	1	2	13
July–September	77	1	–	–	2	–	3	6
October–December...	59	–	1	–	10	1	5	3
	270	1	2	–	14	2	16	29

child who had previously had diarrhoea but was well when examined, had a growth of E. coli strain 0-111 in the intestine. Attention also focuses on the circumstance that the same strain was encountered in 4 other infants of our series who were transferred to the hospital from different institutions. These were not known to have had any noteworthy epidemics of diarrhoea.

In one case was found strain 0-111 and likewise in one case strain 0-26, only after a renewed examination of the stools. Strain 0-44 was seen 5 times only at a later stage without a simultaneous relapse. In two of these cases strain 0-26 had previously been found. If we consider, moreover, that our control series of healthy infants (Table 3) once revealed strain 0-44, the significance of the said E. coli strain as causative agent of infantile diarrhoea becomes questionable. All other strains of E. coli studied by us were not met with in our control material.

Discussion

There has been a considerable and continual incidence of typhoid and paratyphoid fever in Finland (in 1951: 129 and 935 cases respectively), partly as local epidemics, partly as sporadic outbreaks. No classification according to age has been performed in the general statistics. Our investigations have shown that neither of these diseases plays any considerable role in the aetiology of severe infantile gastroenteritis. The occurrence of other bacteria of the Salmonella group is rare in Finland. In our series two infants yielded a finding of Salmonella typhi murium.

Dysentery of the Flexner type has made its appearance in Finland (HELLSTRÖM, HIRVISALO, KOKKO, MUSTAKALLIO). E.g. during the last World War an extensive epidemic occurred in the field army (KOKKO). Sonne-dysentery has not previously been described in Finland. In the course of 1950 when Shigella Sonnei was found in this series, these bacteria were encountered in adults as well (RANTASALO). The said bacteria which were revealed in this

series occurred either towards the end of the second half of the first year of life, or in children older than one year. It has likewise been demonstrated in other series that the disease is not frequently seen in young infants (e.g. COOPER, FURCULOW, MITCHEL and CULLEN). There is, however, the possibility that the significance of bacteria of the Shigella group as a causative agent for the diarrhea is greater in Finland than is shown by our results, since only severe toxic cases are immediately transferred for treatment to our hospital. Attempts are made to start treatment of the milder cases at home, and diarrhoea produced by Shigella usually belongs to this type of disease. According to KOKKO, the chances of recovering Shigella from the stools rapidly dwindle during the second week of illness. In cases three weeks old these bacteria are not found as a rule.

In recent years Escherichia coli strain 0-111 has been described in several countries as causative agent of severe infantile diarrhoea (England: BRAY: BRAY and BEAVAN; PAYNE and COOK; TAYLOR, POWELL and WRIGHT; Holland: BEEUWEKER, CIJSBERTHI and TEN SELDAM; Sweden: FRISELL and LAURELL; LAURELL, MAGNUSSON, FRISELL and WERNER; Denmark: KAUFFMANN and DUPONT; Germany: BRAUN and HENKEL; Finland: GRÖNROOS). In our series there are several individual cases of this strain scattered all over the country, and in addition, one institutional epidemic. It would appear that the strain in question occurs in institutions caring for children (PAYNE and COOK).

Escherichia coli strain 0-55 has been found in England (GILES, SANGSTER and SMITH) and in Denmark (DUPONT; DUPONT and KEISER-NIELSEN). In Sweden only two cases were found by LAURELL. On the basis of our series, the strain does not play any considerable role in Finland.

BIERING-SØRENSEN, KNIPSCHILDT, v. MAGNUS and TULINIUS encountered of E. coli strain 0-26 in diarrhoea patients. This strain has been described in more detail by ØRSKOV. In our series this strain was only seen in children affected with diarrhoea, and similarly with strain 0-111, more frequently in s.c. toxic diarrhoea and in cases which did not simultaneously suffer from respiratory infections. According to our material, Escherichia coli 0-26 is the strain most frequently found in Finland among those studied by us.

Strain 0-44 (BIERING-SØRENSEN *et al.*) was found in our series in association with slight diarrhoea and also in one healthy child who had never been ill with diarrhoea before. In addition, it was met in 5 convalescent patients who did not suffer a relapse with diarrhoea. The significance of the strain as producing infantile diarrhoea is, in our opinion, questionable.

Summary

Results have been given of the occurrence of Salmonellas, Shigellas and Escherichia coli types 0-111, 0-55, 0-44, and 0-26 in the excrements of infants belonging to a series from a Finnish hospital for children. The under-groups of E. coli are not studied.

During the first period in the course of which 259 infants were under treatment (33 of them over one year old) only bacteria of the Salmonella and Shigella groups were studied. They were found in about 5 % of the cases. Two of them were Salmonella paratyphi B and the remainder Shigella Sonnei. These micro-organisms were considerably more abundant in the older children. During the second period which immediately followed the first a study of 270 infants was made who were all under one year of age. Salmonella paratyphi B was demonstrated once and Salmonella typhi murium twice. Bacilli of the Shigella group were not found.

In this group of infants the Escherichia coli type 0-111 was found in 14 patients type 0-55 in 2, type 0-44 in 16, and type 0-26 in 29 patients. E. coli strains 0-111 and 0-26 were found for the most in s.c. toxic diarrhoeas. In the milder forms and particularly in cases simultaneously suffering from a respiratory infection, a positive finding was less frequent. E. coli type 0-111 was recovered from 6 of 8 patients who had fallen ill with diarrhoea at the same orphanage. This strain was more often present in patients transferred for treatment from the various child welfare institutions, although no noteworthy epidemic of diarrhoea had occurred at any of them. The remainder were individual cases scattered all over the country. The Escherichia coli types studied were most often present in infants 3 to 6 months old and least often in infants over 6 months of age. The seasons of the year did not affect the occurrence of these strains in any particular way.

The control series embracing 68 completely healthy children yielded one case of E. coli type 0-44. It was also found in 5 infants recovering from diarrhoea, at a later stage, although the stool specimens had been negative on admission.

On the basis of the results it seems probable that Escherichia coli types 0-111 and 0-26 are to some extent significant in the aetiology of infantile diarrhoea. E. coli type 0-55 was so infrequent in this series that no conclusions are justified with regard to it.

Étude étiologique sur la diarrhée infantile en Finlande.

Cette étude concerne la présence des Salmonellas, Shigellas et Escherichia du type 0-111, 0-55, 0-44 et 0-26 dans les selles d'enfants faisant partie d'un hôpital d'enfants Finlandais. Les sousgroupes de E. coli ne sont pas envisagés. Pendant la 1ère période durant laquelle 259 enfants furent traités (33 étaient âgés de plus d'un an), on étudia seulement du point de vue bactériologique les groupes des Salmonella et Shigella. On a découvert ces germes dans à peu près 5 % des cas. Deux faisaient partie du groupe des Salmonella paratyphiques B. et le reste des Shigella Sonnei. Ces micro-organismes étaient beaucoup plus abondants chez les enfants plus âgés. Pendant la 2e période qui fit immédiatement suite à la 1ère, on étudia 270 enfants tous âgés de moins d'un an. Salmonella paratyphique B fut trouvé une fois et Salmonella typhi murium 2 fois. Les bacilles du groupe Shigella ne furent pas découverts. Dans cette catégorie d'enfants on trouva Escherichia coli type 0-111 chez 14 malades, le type 0-55 chez 2, le type 0-44 chez 16, et le type 0-26 chez 29. Les E. coli 0-111 et 0-26 furent présents, pour la plupart, dans les syndrômes de diarrhée toxique. Parmi

les cas d'intensité moyenne et plus particulièrement parmi ceux qui présentaient une infection respiratoire, la présence de ces germes était moins fréquente. Les Escherichia coli correspondant au type étudié étaient beaucoup plus fréquents chez des enfants âgés de 3 à 6 mois et moins fréquents au-dessus de 6 mois. Nous n'avons pas noté d'influences saisonnières quant à la flore microbienne. Les observations qui nous ont servies de contrôle comprennent 68 cas d'enfants en parfaite santé. Nous n'avons trouvé qu'une fois un des germes étudiés : il s'agissait du E. coli type 0-44. Celui ci fut trouvé également chez 5 enfants convalescents de diarrhée avec un certain temps de recul bien que la coproculture eut été négative lors de l'admission. En se basant sur nos résultats, il semble probable que l'Escherichia des types 0-111 et 0-26 entrent pour une signification importante dans l'étiologie de la diarrhée infantile. On a trouvé si rarement le E. coli 0-55 parmi nos malades que nous ne pouvons tirer aucune conclusion justifiée.

Ätiologische Studien bei kindlicher Diarrhoe in Finnland.

Die Studie beschäftigt sich mit dem Auftreten von Salmonella, Shigella und Escherichia coli der Typen 0-111, 0-44, 0-55 und 0-26 in den Exkrementen von Kindern einer Serie aus einem finnischen Kinderhospital. Die Untergruppen von E. coli wurden nicht untersucht. Während der ersten Periode, in deren Verlauf 259 Kinder behandelt wurden (33 davon über 1 Jahr alt) wurden nur Bakterien der Salmonella und Shigellagruppe untersucht. Sie wurden in etwa 5 % aller Fälle gefunden. 2 davon waren Salmonella paratyphi B und die übrigen Shigella Sonne. Diese Mikroorganismen sind beträchtlich häufiger bei älteren Kindern. Während der zweiten Periode, welche der ersten unmittelbar folgte, wurden 270 Kinder — alle unter 1 Jahr — untersucht. Salmonella paratyphi B wurde einmal und Salmonella typhi murium zweimal gefunden. Bakterien der Shigellagruppe wurden nicht gefunden. In dieser Gruppe von Kindern wurde Escherichia coli Typ 0-111 bei 14, Typ 0-55 bei 2, Typ 0-44 bei 16 und Typ 0-26 bei 29 Patieneten nachgwiesen. Die Colistämme 0-111 und 0-26 wurden meist bei s. g. toxischen Diarrhoen gefunden. Bei milderen Formen und bei Fällen, die mit einer Infektion der Luftwege einhergingen, waren positive Befunde weniger häufig. Die untersuchten Colitypen waren am häufigsten bei Kindern zwischen 3 und 6 Monaten, weniger häufig bei Kindern über 6 Monaten anzutreffen. Die Jahreszeit beeinflusst das Auftreten dieser Stämme in keiner Weise. Die Kontrollserie umfasst 68 vollständig gesunde Kinder, bei denen einmal E. coli vom Typ 0-44 gefunden wurde. Der Befund wurde bei 5 weiteren Kindern nach Genesung von einer Diarrhoe zu einem späteren Zeitpunkt erhoben, obwohl die Stuhluntersuchungen bei der Aufnahme negativ waren. Auf der Basis dieser Ergebnisse scheint es wahrscheinlich, dass die Escherichia coli type 0-111 und 0-26 in gewissem Umfang für die Ätiologie der Säuglingsdiarrhoe von Bedeutung sind. E. coli Typ 0-55 waren so selten in diesen Serien, dass keine Schlüsse darüber gerechtfertigt sind.

Investigaciones etiólogicas sobre la diarrea infantil en Finlandia.

Las investigaciones se han llevado a cabo sobre la frecuencia de hallazgo de salmonelas, shigelas y escherichia coli tipos 0-111, 0-55, 0-44 y 0-26 en las deposiciones de niños que han pasado por un hospital pediatrico finlandés. Los grupos bajos de E. coli no han sido estudiadas. Durante el primer periodo en el curso del cual fueron tratados 259 niños (33 de ellos por encima de 1 año de edad) solo se estudiaron las bacterias de los grupos salmonela y shigela. Fueron hallados un 5 % en estos casos, 2 de los cuales eran paratifus B y los restantes shigelas tipo Sonne. Estos últimos

eran considerablemente mas abundantes en los niños de mayor edad. Durante un 2 período que siguió inmediatamente al primero se estudiaron 270 niños por debajo todos ellos del año de edad. Al paratifus B se halló una sola vez y el bacilo tífico 2 veces. No se hallaron gérmenes del grupo shigela. En este grupo de niños el E. coli tipo 0-111 se halló en 14 pacientes, el tipo 0-55 en 2, el tipo 0-44 en 16 y el tipo 0-26 en 29 niños. Las cepas E. coli 0-111 y 0-26 fueron halladas mayormente en las diarreas tóxicas. En las formas medianas y particularmente en los casos afectos simultáneamente de infección respiratoria los hallazgos positivos son menos frequentes. Los tipos coli estudiados eran mas frecuentes en los niños de 3 a 6 meses y menos en niños por encima de los 6 meses. No había ninguna variación en la frecuencia de estas cepas en relación con las estaciones del año. Las series de control afectaban 68 niños en buena salud en los que se halló una vez el coli tipo 0-24. Se halló asimismo en 5 niños recuperados de su diarrea. Aunque el exámen de las heces había sido negativo en el momento de su admisión. Sobre la base de estos resultados parece probable que el E. coli tipos 0-111 y 0-26 son los que tienen una amplia significación en la etiología de la diarrea infantil, mientras que el tipo 0-55 es tan infrequente en estas series que no justifica ninguna conclusión respecto al mismo.

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Pediatric Clinic
Stenbäcksgatan 11
Helsinki

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From the Department of Pediatrics, University of Pécs,
Pécs, Hungary

The Problem of Oedema in Infantile Malnutrition

by E. KERPEL-FRONIUS and F. VARGA

In contrast to its great frequency in semistarved adults oedema is rather exceptional in wasted infants. Among 380 cases we observed oedema only 8 times, CHOREMIS (5) in 3.1 % of his 450 wasted infants. It thus seems evident that wasting of the body is in itself by no means necessarily linked with the occurrence of oedema.

Infantile malnutrition is, however, a syndrome of inhomogeneous aetiology. There are certain types showing a conspicuous tendency to oedema, such as 1) Czerny and Kellers "Mehlnährschaden". 2) "wartime malnutrition" of infants (2, 7). 3) Tropical forms of malnutrition. 4) Leiner's disease (erythroderma desquamativum). Hence the aetiology of malnutrition has a bearing on the appearance of oedema.

In this paper we endeavour to analyse why oedema is exceptional in spite of severe wasting, in infantile hospital material, as contrasted with semistarved adults and "special" types of infantile malnutrition as enumerated above. We felt that the pathogenic significance of factors generally believed to promote hunger oedema might be tested by their presence in the "oedematous" or by their absence in the "dry" type of infantile malnutrition. We hoped that the relationships between wasting of the body and occurrence of oedema might be further clarified by such comparative work.

This task is facilitated by summarizing some recent brilliant descriptions of oedema in semistarvation (2, 10, 13, 20, 21, 23). Briefly it seems that extensive hypoalbuminaemia doubtless promotes severe, universal oedema. So does elevated venous pressure accompanying hard work, infections or imprudent hypercalorisation. The mechanism of oedema in the latter cases seems to be due to overburdening the wasted heart by rising cardiac output. All this agrees with the classical knowledge on oedema formation (3, 6, 9, 22, 26, 29, 30).

On the other hand, however, oedema has been observed in a great number of semistarved adults even in the absence of important hypoproteinaemia or high venous pressure. The appearance and disappearance of oedema in such cases is clearly linked with posture. The essential departure from the normal

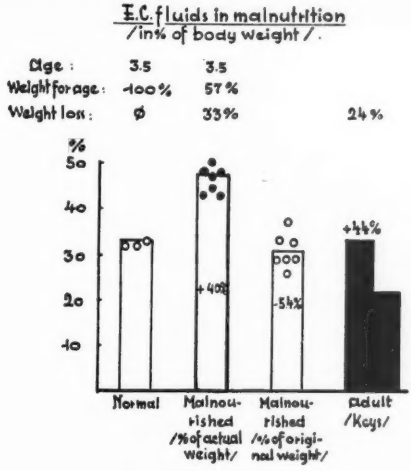

Fig. 1.

is, according to McCANCE, the percentile increase in extracellular body fluid: "the presence in the body of so much fluid free to move under the influence of gravity". In the supine position visible oedema disappears, and this is accompanied by "nykturia". An additional factor conducive to oedema formation is high salt and water intake by semistarved individuals.

Let us now study which of the above-mentioned oedema-promoting factors were absent in our cases of "dry wasting", and present in the few oedematous cases.

The *size of the extracellular fluid compartiment* was found to increase in infantile malnutrition (8, 14, 28.). This is in perfect agreement with conditions found in the semistarved adult (2, 4, 20, 23). Measurements of thiocyanate space may of course sometimes be inaccurate, due to increased permeability of the cells (11). Direct measurements of body water on post-mortem material in malnutrition and the good agreement between direct measurements of body minerals, body water and thiocyanate space during growth (12, 19) seems however to warrant the belief that the data on thiocyanate space are essentially correct.

It is important to point out that the increase in thiocyanate space in infantile malnutrition is only a percentile one; the absolute amount of extracellular fluid is by no means increased.

This is shown in Fig. 1.

The percentage of body weight due to extracellular water (thiocyanate method) can be read from the ordinate scale. 33 % of the body weight of

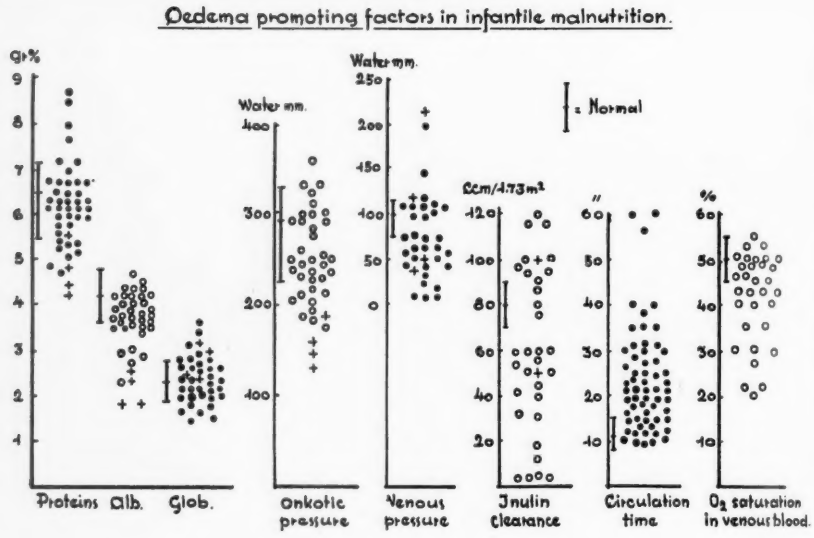

Fig. 2.

normal 3—5 month old infants consists of extracellular fluids. In seven severely malnourished infants of corresponding age, this proportion rises to almost half of the body weight. These infants were all severely emaciated; they were 43 % underweight as compared with infants of the same age, their "weight loss", as calculated from ideal weight according to measured length, was 33 %. If extracellular fluid is related to this reconstructed weight, i.e. to the ideal weight for length, it becomes evident that the absolute amount of extracellular fluid did not increase during wasting, in fact it was somewhat diminished. (Third column of fig. 1.) The same holds true for semistarved adults as shown on the black columns of fig. 1., based on the data of the famous Minnesota experiment (20).

Wasting of the body does not influence the absolute amount of extracellular body fluids. This is spared, while other tissues, fat and muscle, are wasted. In a previous paper (14) we analysed the possible reasons for this peculiarity in wasting.

In figure 2, further factors which may have a bearing on oedema formation are summarized. All cases were severely wasted young infants, their ages ranging between 1—6 months. "Weight loss", as computed from ideal weight calculated from measured length, ranged from 25 to 35 %.

The figure should be read from left to right. The vertical line on each ordi-

nate scale shows the normal range of values found in 8 healthy infants of the same age groups.

The majority of total *serum protein* values (KJELDAHL) fall within the normal range. Most of the *albumin determinations* (precipitation by sodium sulfate and subsequent Kjeldahlization) give low normal values. There are 8 cases with severe hypoalbuminaemia, 4 of which had oedema (crosses) with albumin values between 1.8—2.5 %. Equally wasted infants with mild hypoalbuminaemia, or with normal albumin concentrations were not oedematous. *Globulin concentrations* were mostly in the upper range of normal.

Colloid osmotic pressure was calculated from serum proteins by the formula of KEYS (20). Values found in oedematous cases were near to those seen in the nephrotic syndrome, none of the cases in the normal or low normal range was oedematous.

Venous pressure was low in the majority of wasted infants. It shows, however, a tendency to rise to normal or even high values in cases with secondary infections, especially pneumonia. The higher values in fig. 2 represent mainly such complicated cases. The low venous pressure is believed to counterbalance the oedematous tendency due to osmotic hypotension. The effect of both, as expressed in mm of water, are approximately additive. Thus, oedema should not appear in cases of moderate hypoalbuminaemia when venous pressure is very low. This seems to have occurred in a good number of our cases. In two of them venous pressure was low (50 mm water); the colloid-osmotic pressure, however, fell much more sharply, to 120—150 mm, hence the tendency, to oedema prevailed. In one case venous pressure was doubled (pneumonia) and colloid osmotic pressure the lowest. Oedema was widespread in this instance.

Inefficient kidney function has also to be considered whenever oedema appears. MCCANCE has shown that in semistarved oedematous adults clearances are essentially normal. Other authors (21, 25) found low clearances in some cases where kidney disease cannot be ruled out.

Kidney function in our cases of infantile malnutrition will be analysed in a subsequent paper (15). The following results should only be mentioned here: Inulin and PAH clearances were normal in "dystrophy" and somewhat decreased, or low normal in "atrophy". If these stages of infantile malnutrition are complicated by pneumonia, inulin clearances may be higher than normal for the age of the infant. In the severest stage of malnutrition, in athrepsia, anhydraemia appears (16) and consequently clearances are as low as in any other case of dehydration. Hence the wide scatter in our material composed of different "stages" of malnutrition.

The low clearances may be responsible for the appearance of transitory oedema if great amounts of salt and water are given to severely emaciated

and dehydrated infants. Oedema may occur in spite of rising clearances due to improving circulation, because it takes some time before normal kidney function is reestablished. In such cases, of course, other factors may also contribute to oedema formation; venous pressure may rise, and osmotic hypotension, up to now masked by dehydration, may become manifest.

Diminished kidney function is clearly connected with slowing of systemic circulation (decreased cardiac output) so characteristic of the severest stages of infantile malnutrition (15, 16, 17).

Another possible cause of oedema formation is *increased capillary permeability*, induced perhaps by stagnant anoxia due to slow circulation (fig. 2). In athrepsia venous O_2-saturation may indeed decrease, rarely, however, to the values seen in infantile toxicosis (18). In an earlier work we found, using the method of Landis, an increased capillary permeability (17). Correspondingly, GOLLAN described an accelerated disappearance-rate of intravenously administered dyes. In spite of evidences of increased capillary permeability, these wasted infants had not been oedematous, hence this does not seem to be an important aetiological factor in hunger-oedema.

Discussion

We may briefly summarize by saying that oedema was exceptional in our wasted infants because, in spite of considerable loss of weight, oedema-promoting factors were absent in the majority of these cases. First, extreme osmotic hypotension was rare, because extreme dietary protein deficiency was exceptional. An analysis of the origin of malnutrition revealed that, although more than sixty percent of all cases were wasted because of inadequate caloric intake, extreme protein dificiency ("Mehlnährschaden") occurred in six percent of the cases. The deficiency in calories resulted mainly from with-helding sugar from markedly diluted milk formulas; in many instances the supply of mother's milk was insufficient and no additional food was given. In 25 % a correct formula had been given and wasting followed infections. In 6 % congenital abnormalities led to wasting.

A further reason for the absence of hypoalbuminaemia was that in severest malnutrition anhydraemia often masked the loss of circulating plasma protein invariably occurring in "athrepsia".

This is shown in figure 3. Plasma volume was measured by Congo red dye, serum protein by Kjeldahl's method.

The material presented is divided in two groups. In the first "weight loss", calculated from ideal weight computed from measured length, was less, in the second group more than 30 % of this "reconstructed" weight.

Black circles represent grams of circulating proteins per kilog. ,i.e. wasted,

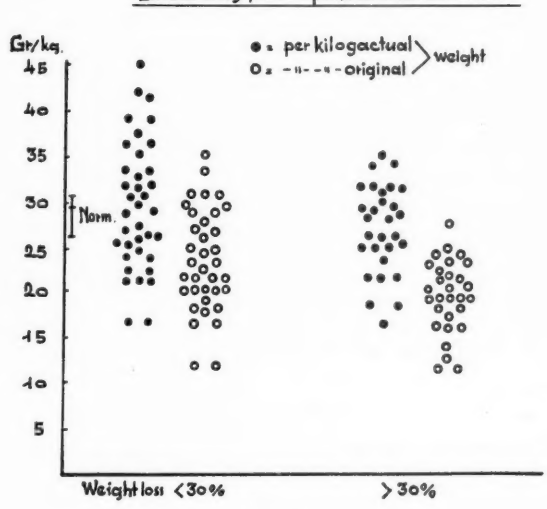

Fig. 3.

weight, white circles per kilog. of reconstructed weight. The vertical line near the ordinate scale shows the normal range for circulating proteins for the same age. In group I circulating proteins are high per kilog. "wasted weight" in a good number of cases. When referred to "reconstructed weight", it is clear that in approximately half of the cases plasma proteins were not wasted, hence they appeared to be high per kilog. "wasted weight". The same holds true for semistarved adults (Minnesota experiment) and similar results were described by GOLLAN (8) and THURAU (31) in malnourished infants of comparable severity.

In the second group, circulating plasma proteins are apparently normal per unit of "wasted weight" and low per unit of original "reconstructed weight". — Thus, very severe malnutrition attacks plasma proteins. If their concentration appears to be normal that is often due to dehydration (low plasma volume, high haematocrit and R.B.C.-readings). Dehydration, when complicating malnutrition, accelerates its course, hence the frequency of very severe wasting in cases complicated by diarrhoea. The frequent occurrence of dehydration, often induced in our material by dyspepsia coli infection, is one of the factors inhibiting the tendency to oedema in severely malnourished infants. In contrast to the semistarved adult, where high salt and water intake often aggravates oedema, in severe infantile malnutrition loss of salt and water is more frequent.

Oedema may, however, occur in the semistarved adult even in the absence of hypoalbuminaemia. This type of oedema is sometimes induced by elevated venous pressure following hard work, infections or hypercalorisation. The first possibility, of course, does not arise in infants, the other two may, however, occur (fig. 2.), although more frequently venous pressure is low, thus counterbalancing the effects of milder osmotic hypotension.

The percentile increase of extracellular fluid in the wasted body may lead to oedema in the adult, as already pointed out, without osmotic hypotension or elevated venous pressure. As this type of oedema is postural in its origin, it plays no role in infants lying in recumbent position, although the percentile increase in extracellular fluids is always present.

Briefly, oedema was rare in our malnourished infants because severe osmotic hypotension was exceptional, elevated venous pressure rare, salt and water losses frequent, and because in infants effects of posture are not operative.

There are, however, as told on the first page of this work, particular types of infantile malnutrition in which oedema is common. All, excepted Leiner's disease, are of the "Mehlnährschaden" type of malnutrition, sometimes complicated by avitaminosis (1, 33.). In all cases hypoproteinaemia is found. Decrease of the secretion of pancreatic ferments seems to be a further feature of this conditions. In atrophy due to Leiner's disease hypoproteinaemia is certainly due to decreased pancreatic ferments connected with cystic fibrosis of the pancreas (24) and to loss of proteins through the reddened and desquamating skin (7). The same might be true for the tropical forms of malnutrition.

All these particular hypoproteinaemic types of malnutrition are frequent in war-ridden and tropical countries. They are rather exceptional in present day hospital material in Europe, hence the rarity of oedema in infantile malnutrition, mainly linked with hypoproteinaemia.

Summary

In contrast to the semistarved adult in our material of severely wasted infants oedema occurred only in about 2 % of all cases. Oedema was conspicuously rare in this material because severe hypoproteinaemia and osmotic hypotension were exceptional, elevated venous pressure rare, dehydration frequent and because renal clearances were very low only in cases complicated by dehydration. Although extracellular body fluid increases percentually, this does not promote oedema formation because in infants effects of posture, i.e. gravity, obviously do not operate. The aetiology of malnutrition in infancy has a bearing on oedema formation inasmuch as the latter is frequent in those type in which hypoproteinaemia is apt to develop; such types are the following: "Mehlnährschaden", "wartime" and "tropical" malnutrition, and Leiner's disease. The latter types of "hypoproteinaemic" malnutrition are rather exceptional in present day hospital material hence the rarity of oedema.

Le problème de l'oedème dans la sous-alimentation du nourrisson.

Contrastant avec ce qui se passe chez l'adulte sous-alimenté, dans nos cas de nourrissons sévèrement atteints, l'oedème survint seulement dans environ 2 % des cas. L'oedème était de toute évidence rare dans ces cas parceque l'hypoprotéinémie et l'hypotension osmotique étaient exceptionnelles, la pression veineuse rarement augmentée, la déshydratation fréquente et parceque la «clearance» rénale était très basse seulement dans les cas compliqués de déshydratation. Bien que le liquide extracellulaire augmente proportionnellement, ceci ne provoque pas de formation d'oedème parceque chez le nourrisson, les effets de posture — c'est à dire la pesanteur — ne comptent évidemment pas. L'étiologie de la sous-alimentation dans la première enfance a un substratum dans la formation de l'oedème pour autant que ce dernier est fréquent dans ces cas oú l'hypoprotéinémie est capable de se développer; ce sont les suivants: dyspepsie des farineux, sous-alimentation «de guerre» et «tropicale», et maladie de LEINER-MOUSSUS. Ces derniers types de sous-alimentation «hypoprotéinémique» sont tout à fait exceptionnels dans la clientèle hospitalière actuelle d'oú la rareté de l'oedème à l'hôpital.

Das Ödemproblem bei der kindlichen Unterernährung.

Im Gegensatz zu halbverhungerten Erwachsenen treten in unserem Material bei schwer abgezehrten Kindern Ödeme nur in etwa 2 % aller Fälle auf. Ödeme waren in diesem Material auffallend selten, weil schwere Hypoproteinämien und Hypoonkie ausnahmsweise, erhöhter Venendruck selten, Dehydration häufig vorkamen, und weil die Nieren-Clearence nur bei durch Dehydration komplizierten Fällen sehr niedrig lag. Obwohl die extrazelluläre Körperflüssigkeit prozentual ansteigt, führt sie nicht zur Ödembildung, weil bei Kindern der Einfluss der Körperhaltung, d. h. der Gravität offensichtlich keine Rolle spielt. Die Ätiologie der Atrophie spielt insoferne eine Rolle bei der Entstehung von Ödemen, als letztere nur bei Typen, welche zur Hypoproteinämie neigen, häufig sind. Solche Typen sind: „Mehlnährschaden", „Kriegs-" und „Tropen-"Unterernährung und die Leinersche Erkrankung. Die letzteren Arten von „hypoproteinämischer" Unterernährung sind heutzutage im Krankenhausmaterial selten, deshalb auch die Seltenheit der Ödeme hier.

Problemas sobre en la malnutrición infantil.

En contraste con la desnutrición del adulto en nuestro material de niños severamente afectados el edema ocurría solo en un 2 % de casos. Esta aparición poco frecuente del edema era debida a que la presencia de hipoproteinemia y disminución de la presión oncótica eran excepcionales, la presión venosa raramente era elevada, la deshidratación frecuente y el aclaramiento renal era muy bajo solo en los casos complicados con deshidratación. Aunque el agua orgánica extracelular aumente en su relación procentual, ello no provoca edema a causa del efecto postural en los niños. La etiología de la malnutrición en la infancia guarda una posición en relación con el edema en tanto que éste es frecuente en los tipos en los cuales hay hipoproteinemia, como lo siguiente: «distrofia farinácea», «edema de guerra» y malnutrición «tropical» asi como enfermedad de Leiner. El último de malnutrición hipoproteica son excepcionales en el material hospitalario actual así como el edema mismo.

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Department of Pediatrics
University of Pécs
Pécs. Hungary.

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CASE REPORTS

Anaemia Hypoplastica Congenita (Anaemia Typus Josephs-Diamond-Blackfan). Report of a Case Treated with Adrenocorticotropin with Effect

by ARNE KÅSS and ALFRED SUNDAL

(From the Pediatric Clinic of the University Hospital in Bergen. Chief: Professor Alfred Sundal)

Anemias due to a deficient function of the bone marrow most frequently are of the secondary type, provoked by a suppression of the normal bone marrow by inactive, pathological tissue or by an actinic, infectious, toxic or allergic injury of the marrow. Less frequent is failure due to exhaustion of the bone marrow. A splenogenic inhibitive mechanism may also produce the same peripheral blood picture as marrow injury in spite of a pronounced marrow activity.

Of the aplastic-hypoplastic anemias — also called refractory anemias because they resist any form of treatment other than blood transfusions — the idiopathic forms are far less frequent. These types mainly occur in infancy and adolescence. The idiopathic aplastic anemia is most frequently seen among older children, the anemia hypoplastica congenita, on the other hand, belongs to the pathology of infancy, and since it was described by DIAMOND and BLACKFAN in 1938, is considered as a nosological entity.

The disease entity was based on 4 observed cases described as a chronic, slowly progressive anemia with a protracted course. It appears shortly after birth and is presumably a congenital disorder. The anemia is prone to be accompanied by a moderate leucopenia and thrombopenia but without a haemorrhagic diathesis. The bone marrow presents hypoplasia mainly involving the erythropoietic elements, and in the peripheral blood there is a small number of reticulocytes. The patients are dependent upon a regular blood supply by transfusions from the age of a few months. Unexplained and permanent remissions may be seen.

The classical, prominent features described by BLACKFAN and DIAMOND are found in the casuistics of all authors that later have studied this disease. Further variations in the course have been observed and, in addition, abundant supplementary informations given regarding laboratory findings and other observations together with several therapeutic attempts.

Own case

Girl E. K. N., born 29.7. 1948. From November 1948 to June 1950 she was observed regularly in the Epidemic Department, and later in the Pediatric Clinic of the University Hospital in Bergen.

The patient is the only child, the parents are healthy. No family history of anemia. Pregnancy normal. Birth forceps delivery, one week after term. Birth weight 5250 g.

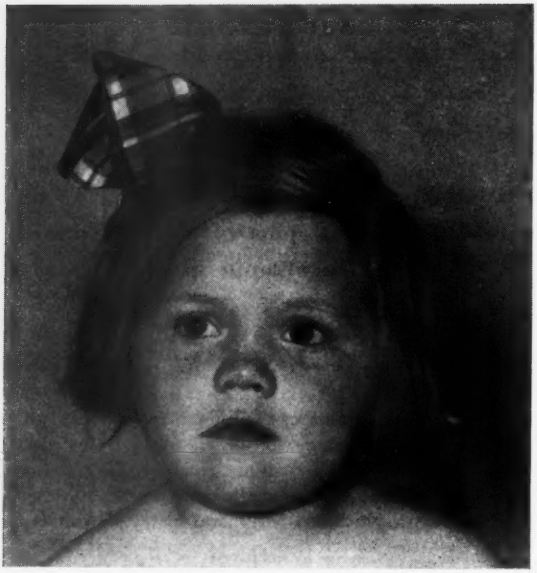

Fig. 1. Patient E. K. N. Age $3\,^{10}/_{12}$ years.

Length 50 cm. Before the first admission to hospital she received supplementary feedings of breast-milk and cow milk formula and vitamins. The child always has been pale. At 2 months she had mild diarrhoea for a few days. A physician administered Entero-Vioform, $^1/_4$ tabl. 4 times during one day. Later the mother herself gave the same tablets on 2 or 3 occasions. In all she had 3 or 4 tablets. The patient has been healthy until the last few days before admission to hospital, when she developed feeding difficulties.

On *admission* (4.11.48) at the age of 3 months, the patient was extremely pale with a colour of the skin and mucous membranes like that of alabaster. No fever. No skin bleedings. No enlargement of lymphatic nodes. The liver could be felt about 3 cm under the right costal arch, and the spleen was just palpable. Her muscular activity was great. Hb 24 per cent, r.b.c. 0.96 mill., white b.c. 3,600. Differential count: young nucleated 1 per cent, segmented 11 per cent, lymphocytes 87 per cent, monocytes 1 per cent.

A few hours after admission she had a blood transfusion. A second transfusion was performed with administration of iron and liver preparations a few days later. A distinct rise in the reticulocyte count occurred reaching 3.7 per cent. A spontaneous remission of the anaemia occurred. The white blood picture still revealed a striking granulocytopenia with 92—98 per cent of mononucleated cells, mainly lymphocytes. Bone marrow 8.11. 1948: "Cell poor preparations with a normoblastic erytropoiesis. Scanty myelopoiesis. Numerous lymphocytes and abundant reticulum cells." A second marrow examination (13.12. 1948) showed "scanty erythropoiesis and myelopoiesis, many lymphocytes (>50 %) and some reticulum cells."

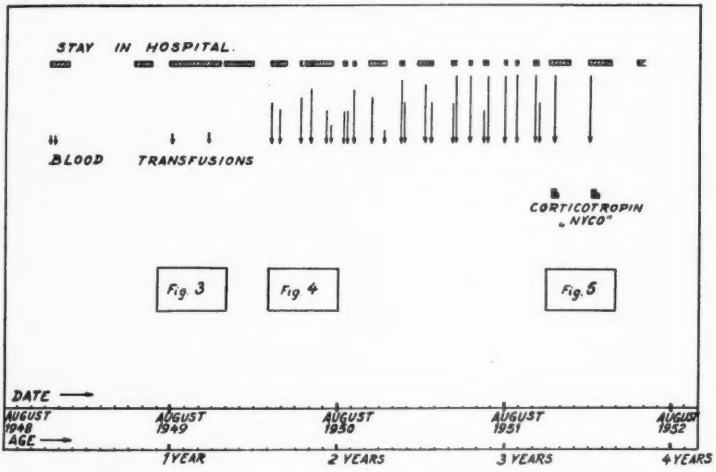

Fig. 2.

For the next half year the patient was observed and she did not develop any anaemia, but she constantly suffered from the granulocytopenia.

On *re-admission*, at 11 months, she had a rhinopharyngitis with fever. The liver and the spleen were enlarged as before. The white blood picture presented a more varied condition during the fever, with myelogenic cell counts amounting to 25 per cent. Reticulocytes 0.5—0.8 per cent.

During the next month the anaemia became marked, and at about one year, she was *readmitted* for a bloodtransfusion. On examination the granulocytopenia was still present in the peripheral blood; the marrow was cell-poor with a marked abundance of lymphocytes and mostly low reticulocyte counts, but still ranging between 0.3 and 1.7 per cent.

At 16 months she was readmitted owing to a stridorous laryngitis. The anaemia was moderate, normochromic (Hb about 70 per cent). The reticulocyte counts: 0.3—1.2 per cent. During the acute fever counts up to 30 per cent granulocytes were found in the peripheral blood which shortly afterwards were predominated by myelogenic cells in different stages of development, whereas the erythropoiesis still was scanty.

At the age of 20 months the patient was *readmitted:* Hb 26 per cent, r.b.c. 1.62 mill., white b.c. 3,400 with 92 per cent lymphocytes. The patient was pale, but only a little exhausted. The liver was palpable about 5 cm under the right costal margin. The spleen was felt 3—4 cm, under the left costal margin. A blood transfusion was administered and liver and iron treatment was continued. Reticulocyte counts 0.1—0.2 per cent. On dismission the haemoglobin rate was 68 per cent, r.b.c. 3.2 mill. per cmm.

Four weeks later the patient was readmitted because of the anaemia symptoms, viz. pallor, anorexia and a mild degree of lassitude. The spleen was smaller, other clinical and haematological findings were unaltered. The reticulocytopenia was even more marked with counts from 0 to 0.1 per cent on several examinations. There was no rise following vit. B_{12} (Rubramin 0.5 ml every second day, for 6 injections). A transfusion was necessary every 4 weeks.

TABLE 1

	1950			1951						1952	
	June	Nov.	Dec.	Febr.	Apr.	June	July	Nov.	Dec.	Jan.	March
Icterus index	3			6	3						
Thymol reaction (units)	10			2.1	2.8		2.6		5.5	2.0	
Serum iron (γ%)	178			153	248	180		281			
Nonprotein N (mg%)	68			41							
Protein in plasma (g%)											
Total protein	8.03	7.40	6.86	5.23		7.07					
Albumin	4.63	4.78	4.45	3.41		4.27					
Globulin	3.40	2.62	2.41	1.81		2.80					
A/G	1.4	1.82	1.85	1.87		1.53					
Formolgel	–										
Total cholesterol (mg%)					157						
Sodium (serum) (mg%)								302			
Potassium (serum) (mg%)								20			
Osmotic resistance	norm										
Coombs' test	–										–

The patient was transferred to the Pediatric Department of the University. On examination at this clinic, the findings were the same as before: a pale, somewhat stout and flabby girl, with a psychical development corresponding to her age. No fever, no skin bleedings, but some pyodermic efflorescences in the buttocks. The liver and the spleen were moderately enlarged. Hb 62 per cent, red blood cells 3.42 millions (blood transfusion two days before). White b.c. 3,800 with 8 per cent granulocytes. Reticulocytes 0.3 per cent.

The patient now received blood transfusions at intervals of 4 to 6 weeks, and she was admitted to the Pediatric Clinic 14 times during the following $1\frac{1}{2}$ years. During this time supplementary examinations were performed.

In the serum no pathologic antibodies could be traced, and there was nothing to indicate an influence of incomplete antibodies on the red corpuscles. Differential agglutination test after transfusion would have been of value, but it was impossible to perform owing to the blood groups of the patient: O, MN, Rh—.

Bone marrow samples have been examined several times and showed alterations after treatment, until the later reported: i.e. scanty and normoblastic erythropoiesis. The myelopoiesis frequently showed less activity than normal, and on the whole the bonemarrow picture gave the impression of a certain inhibition of the maturation process with relatively few mature cell types. A constant finding was the abundance of lymphocytes.

During the whole time of observation the patient had continued to develop physically and mentally. She behaved naturally, except for the periods of rapidly falling blood values when she had a bad appetite and was fretting, thus indicating to the parents that the time for a new transfusion was approaching.

On physical examination constant findings have been a palpable liver about 3 cm. under the costal margin, and the spleen palpable about 2 cm. under the costal margin. No enlargement of the lymph nodes nor skin bleedings have seen observed.

Treatment

The patient was, as mentioned before, from the age of 1 year dependent on regular bloodtransfusions with intervals of about 4 to 6 weeks. The blood values previous to the transfusions fell to somewhat varying figures: Hb 40—65 per cent, red blood cells 2.05—3.54 mill. The first time 20 ml citrate blood per kg body weight was administered, and later suspensions of blood corpuscles composed of 500 ml citrate blood (the body weight was now 16 kg) from which 220—260 ml plasma had been withdrawn and to which Ringer's solution had been added as dilution fluid to about 425 ml. After these transfusions a somewhat greater immediate increase in the blood values was stated, but there was no evident increase of the intervals between the transfusions.

Apart from a rather transitory and moderate increase in the reticulocytes up to 2 per cent after daily injections of a liver preparation (Pernami), in June 1950, i.e. at the age of 2 years, the patient showed almost permanently low reticulocyte counts, e.g. from 0.3 to 0.4 per cent.

Following the reported reticulogenic effect of ACTH, we started with the first series with ACTH injections (Corticotropin Nyco) during the time from 10.11 to 26.11 1951 (cf. Curve for dosage). The blood counts after transfusion on the 16.11 were: Hb 86 per cent, red blood cells 4.25 mill. 9 days after the treatment was started, a new rise in the reticulocyte count with a maximum of 3.4 per cent was observed. The rise persisted for 3 weeks after discontinued treatment, 1.3—2.2 per cent; and the blood values were unchanged from the time of transfusion 5 weeks before. (Hb 90 per cent, red blood cells 4.16 mill.) The patient was sent home, which lies more than a day's journey from the hospital, and on admission 7 weeks after the treatment had been finished, she had a moderate anaemia with Hb 71 per cent, red b.c. 3.19 mill., but reticulocytes were still 0.4—0.6 per cent, thus, higher, than before ACTH treatment.

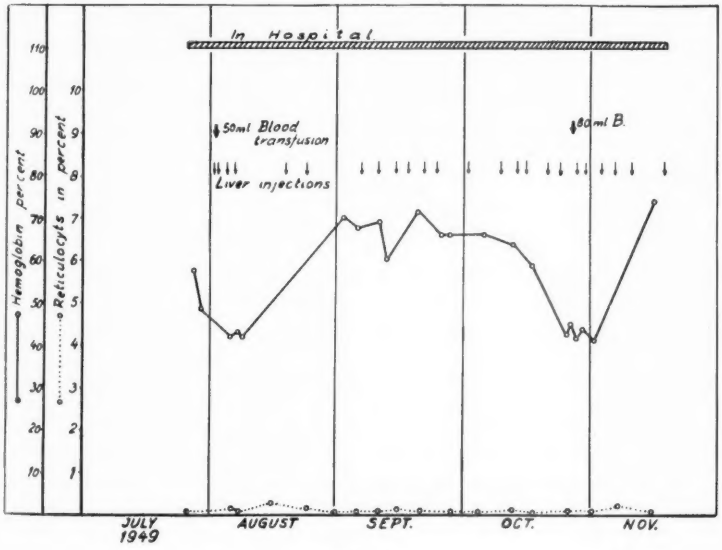

Fig. 3.

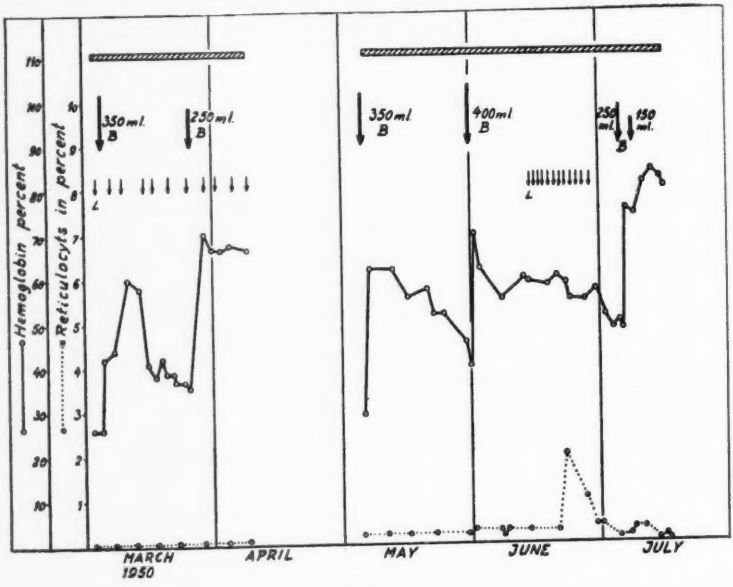

Fig. 4.

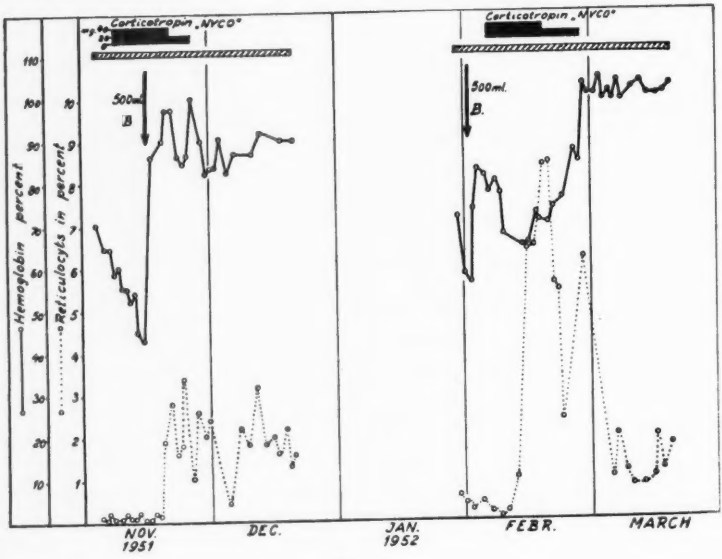

Fig. 5.

On admission 25 ml blood was withdrawn from the patient in order to perform further blood examinations. This caused a marked fall in the blood values (60 per cent, 2.58 mill.) and a transfusion was given 15 weeks after the preceding one, thus with an interval of about three times longer than usual. After this transfusion she had Hb 74 per cent and red blood cells 3.43 mill. (2.2.52).

A second ACTH course from 6.2 to 28.2.52 rendered a similar response with a sudden and marked rise in the reticulocyte count from the 9th day, viz. 6.4 per cent. As will be seen from the curve, the rise prevailed during the following weeks, and the patient presented a spontaneous increase in the blood values, on the 19.3.52 amounting to 93 per cent Hb and 4.02 mill. red blood cells.

A bone marrow examination directly after the first course had been discontinued, 6.12.51, revealed a striking alteration compared with previous examinations, the normoblastic erythropoiesis with numerous macroblasts, appeared relatively rich in proportion to the total cell count. There was also a brisker myelopoiesis, consistent with the more varied peripheral blood picture after treatment. Repeated marrow examination on the 29.1.52, — just before the second course was begun, — revealed preparations containing an ordinary number of cells, with a scanty erytropoiesis, but with a striking prevalence of lymphocytic cells, which was a usual finding on previous examinations.

The patient again was dismissed and was controlled 1 month later, 28.3.52: Hb 86 per cent, red blood cells 3.64 mill. and reticulocytes 1.2 per cent. Two months after the second ACTH treatment, 26.4.52, the figures were: Hb 74 per cent, red bl.c. 3.29 mill., reticulocytes 0.6 per cent. Thus the patient 12 weeks after the last transfusion only had a moderate anaemia and had no further need for blood.

Discussion

Our patient is a now about 4 years, and is said to have been pale from birth. At 13 weeks she was admitted to hospital with a marked anaemia. There was a normochromic anaemia, pronounced granulocytopenia and a sparse erythropoiesis and myelopoiesis in the bone marrow preparation. The first time the possibility of an agranulocytosis due a toxic cause was discussed, in view of the repeated administration of small doses of an intestinal desinfectant. The patient was treated with blood transfusions iron- and liver preparations and responded with a rise in the reticulocyte count and recovery of the anaemia. The peripheral blood picture and blood marrow preparations were still pathological, and for a time a leukaemic condition in remission was feared.

During the first year of life, the patient developed an anaemia which necessitated blood transfusions with increasing frequency, and at the age of 11 months she presented the typical features of an anaemia hypoplastica congenita (anaemia typus Josephs-Diamond-Blackfan).

All previously reported cases at the age of a few weeks or months seem to have presented a fully developed failure of the blood regeneration process by the time the anaemia was diagnosed. Our patient at this stage possessed the ability to respond with an increase in the reticulocyte count, but the later course, including clinical and haematological features, correspond to the usual description of the disease.

The patient in spite of her anaemia has shown a natural physical and mental development. The anaemia is normochromic, accompanied by a distinct failure on the part of the reticulocyte values, and the patient needed regular blood transfusions

at an interval of 4 to 6 weeks, from the age of 1 year when the condition became fully developed. The peripheral blood picture was characterized by a normal white cell count, but on differential counting there was a striking granylocytopenia. These features as well as the hypoplastic erythropoiesis and abundance of lymphocytes, have been reported previously in connection with this disease.

All the time our patient has presented a moderate, but distinct enlargement of the liver and spleen. The size of the spleen has not increased, but the liver is possibly relatively more enlarged than on the first examination and has also a firm consistence. Hepatosplenomegaly may be found in all types of anaemia in infancy as evidence of extramedullary erythropoiesis. Later the enlargement of the liver and spleen has been considered as a sign of the haemosiderosis as a result of the frequent blood transfusions. The application of concentrated blood cell suspensions should increase the risk of this complication. The patient, however, presents no evidence of lymphnode or skin involvement in support of this possibility. The patient got in all 30 transfusions i.e. 10,300 ml blood.

All the time she has shown normal thrombocyte counts and there has been no signs of a haemolytic mechanism. During infections there has been a transitory but distinct rise in the myelogenic cell count in the peripheral blood.

Previously no successfull treatment has been described, except the symptomatic blood transfusion treatment. ACTH is said to have a reticulogenic power, but, except for a case mentioned by STURGEON and dying during the treatment, the application of the hormone in cases of aplastic or hypoplastic anaemias in infants has not been reported. Our patient responded to treatment with two courses of ACTH with a marked rise in the reticulocyte count and a spontaneous remission of the blood values. The last three years preceding the treatment, the patient had been controlled regularly, presenting reticulocyte counts almost constantly less than 0.5 per cent, except for the transitory moderate increase after daily injections of liver preparations. (Cf. Table.) Nine days after the first course of ACTH treatment was started, a rise in the reticulocyte count to 1.8 per cent was observed, increasing to 3.4 per cent during the subsequent 5 days. These satisfactory reticulocyte counts were still increasing the following month. Nine days after starting the second course with ACTH treatment a similar response occurred with rise in the reticulocyte count to 6.4 per cent, and at the end of the control-period 5 weeks later it was 1.8 per cent. After the first course the transfusion interval was increased from 4—6 weeks to 15 weeks, and after the second course 12 weeks have now been passed since the last transfusion. The anaemia is again developing and the reticulocyte count has fallen to a level below the limits of normal values.

On the basis of the marrow culture studies of CATHIE, it must be assumed that the ACTH medication directly or indirectly is acting on the inhibition of the maturation at the normoblast-reticulocyte stage. The bone marrow will now be able to supply fully finished products and will respond with a brisk erythropoiesis as shown in our patient after ACTH treatment.

The treatment is only effective for a short time. We tried two series of ACTH treatment hoping that we could place the patient in a permanent full remission, or, at any rate stabilize the anaemia. However, this hope has been unfulfilled, and now we are using Depot ACTH (long-acting ACTH) with 1 to 2 weekly injections, hoping that we can attain the same results as in other cases susceptible to ACTH treatment.

Summary

A case of anaemia typus Josephs-Diamond-Blackfan in a 4 year old girl has been described. She has been dependent on regular blood transfusions with short intervals, most frequently of 4—6 weeks. The clinical features were typical, with a marked reticulocytopenia as the most striking haematological finding. After two courses with ACTH treatment was a marked increase in the reticulocyte count, both times occurring on the 9th day after starting the treatment, with a duration of several weeks, accompanied by a spontaneous remission of the blood values, and thus the intervals between the transfusions have been prolonged for 15 weeks.

Anémie hypoplastique congénitale (anémie du type Josephs-Diamond-Blackfan) traité par l'ACTH avec effet favorable.

Un cas d'anémie du type Josephs-Diamond-Blackfan survenue chez une fille de presque 4 ans est décrit par l'auteur: Cette affection nécessitait des transfusions régulières à courts intervalles: tous les 4 à 6 semaines au minimum. Le tableau clinique était typique avec une réticulopénie marquée qui était le trait hématologique le plus frappant. Après 2 traitements par l'ACTH, il y eut une élévation marquée du nombre de réticulocytes apparaissant les 2 fois le 9e jour après le début du traitement et durant plusieurs semaines, accompagnée d'une rémission spontanée de la valeur globulaire. Ceci eut pour conséquences que les transfusions purent n'être faites qu'à 15 semaines d'intervalle.

Erfolgreich mit Adrenocorticotropin behandelten Fall von angeborener hypoplastischer Anämie (Typ Josephs-Diamond-Blackfan).

Beschrieben wird ein Fall einer Anämie vom Typus Josephs-Diamond-Blackfan bei einem fast 4 Jahre alten Mädchen. Sie war auf regelmässige Bluttransfusionen im Abstand von 4—6 Wochen angewiesen gewesen. Die klinischen Zeichen waren typisch, eine deutliche Reticulopenie war das hervorstechendste hämatologische Zeichen. Nach 2 Behandlungen mit ACTH kam es zu einer deutlichen Zunahme der Reticulocyten, beidemale am 9. Tag nach Beginn der Behandlung. Diese Zunahme dauerte einige Wochen und war mit einer Spontanremission der Blutwerte verbunden; als Folge dieses Effektes konnten die Intervalle zwischen den Bluttransfusionen auf 15 Wochen verlängert werden.

Anemia hipoplástica congénita (Anemia tipo Josephs-Diamond-Blackfan). Presentación du en caso tratado con buenos resultados con adrenocorticotropina.

Se describe un caso de anemia de tipo Josephs-Diamond-Blackfan en una niña de casi 4 años de edad. Se le habían estado haciendo transfusiones regularmente con cortos intervalos, frecuentamente de 4 a 6 semanas. El cuadro clínico era típico con una marcada reticulopenia como hallazgo hematológico mas saliente. Tras dos series de tratamiento con ACTH se apreció un notable aumento en el recuento de reticulocitos, ambas veces ocurriendo 9 días después de terminar la medicación, con una duración el efecto de varias semanas, acompañado de una expontánea remisión de las alteraciones hematológicas, hasta el punto que la práctica de transfusiones pudo prolongarse a un intervalo de mas de 15 semanas.

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Barneklinikken
Haukeland Sykehus
Bergen. Norway

A Case of Reticulo-Endotheliosis with Unusual Course

by SVEN TÖRNQVIST

(*From the Department of Paediatrics, Norrköping Hospital. Head: Gustaf Lindberg, M. D.*)

The case of reticulosis which is to be described, although not furnishing fresh evidence as to the classification of granulomatous diseases of the reticulo-endothelial system or the aetiology of such conditions, nevertheless would seem to be of interest owing to its unusual course.

Record No. 764/1951, L.E.K. On 23.2. 1951 a boy, born on 1.1. 1949, was admitted to the Department of Paediatrics at the Norrköping Hospital. The patient, an only child, had previously been healthy. He had a normal development and was able to walk when he was 13 months old. Early in January, 1951, his parents had noticed that the boy was walking with a limp. Having suffered a mild injury he was subjected to medical examination including roentgenograms of the hip joints taken on 30.1. 1951 and these were all normal. When admitted to hospital on February 23rd, the patient was found to walk stumblingly and to need support. His condition was normal in other respects. There was no fever, S.R. was 48 mm, Hb. 90 %, R.C. 4 760 000, W.C. 4 000 (neutrophils 10 %, lymphocytes 87 %, and monocytes 3 %). Pulmonary x-rays, N.A.D. Spinal puncture, normal findings. At the request of the parents the patient was discharged on 10.3. 1951 before a diagnosis had been made or the impediment in walking explained. His general condition was practically unchanged.

On 8.5. 1951 he was re-admitted after having been treated at home during the interval. Occasionally he had had fever attacks which were quite transient. Since the end of April he had a cough and fever. On admission on May 8th his general condition had deteriorated. The temperature was 40°.5 C., the skin was pale, and the muscles of both legs were atrophic. Mucosa pale. Pea-sized lymph nodes in the neck, axillae, and groins. On palpation the *spleen*, which was firm to the touch, was found to extend downwards to the umbilical plane. Both patellar reflexes were positive. Hb. 26 %, R.C. 1490000, W.C. 2200. The patient was instantly given a blood transfusion and aureomycin. S.R. was 68 mm. *X-ray examination* on 10.5. 1951: Skull and thoraco-lumbar spine, no pathologic changes. Lungs: Within an area of hazelnut size and corresponding to the first intercostal space on the right side shotty parenchymal densities were noted. *Bone marrow puncture* on 16.5. 1951: Comparatively cellular specimen. The normal structure is completely obliterated. The picture is dominated by lymphocytes and lymphoid reticulum cells. Diagnosis, panhaemophthisis. Agranulocytic picture. Incipient, leukaemic reticulosis with lymphatic differentiation (Dr. N. G. Nordenson). From 8.5. to 30.5. 1951 low platelet rates, lowest on 11.5. viz. 27000. Otherwise no clinical evidence of haemorrhagic diathesis. Blood transfusion was twice repeated; in addition the patient was given iron, liver preparations, and vitamin B_{12}. Aureomycin was administered during pyrexial periods. The haematological findings showed improvement which proceeded until entirely normal rates were observed towards the end of June. The differential white count repeatedly disclosed an eosinophilia up to 15 %. The general condition also improved. Towards the end of June the spleen had receded to the lower thoracic aperture, and simultaneously the impediment in walking had subsided so that the patient was able to walk without support. The boy was discharged on 19.7. 1951 with still normal blood values. S.R. was 10 mm. However, at that time the spleen had once more increased in size, and there was also hepatic enlargement. In the retromandibular fossae lymph nodes of more than bean size were felt on palpation. Considerable valgus position of both legs. The gait was practically unimpaired.

At discharge on 19.7. 1951 the diagnosis was still obscure. In the first place lymphatic leukaemia with atypical course and spontaneous remission was considered as a possibility.

Owing to the pyrexia and increasingly impaired general condition the patient was again re-admitted on 25.7. 1951. On admission the spleen was found to have increased more in size, viz. extending downwards as far as the groin. The lower margin of the liver was felt in the umbilical plane. The lymphoglandular enlargement in the retromandibular fossae had also increased since the previous hospitalization. The blood values were practically normal. S.R. was 35 mm. Aureomycin, which previously had proved efficacious against the pyrexia, was administered. The fever subsided, and after some few days the patient's temperature was normal. His condition deteriorated rapidly, however, and he died on 7.8. 1951.

Autopsy disclosed no abnormality of the thoracic organs. The liver, weighing 1 130 g, was pale and firm. The spleen weighed 730 g, was pink in colour and viscid in cross-sections. The left kidney weighed 220 g, the right one 180 g. A haemorrhagic area was noted in the right renal capsule.

Microscopic examination. The material forwarded for examination includes a *lymph node* of nearly hazelnut size. The lymphoid structure of this node is practically obliterated. In the marginal zone, especially, there are very indistinct, round formations, probably remnants of germ centres. The marrow of the lymph node contains dense,

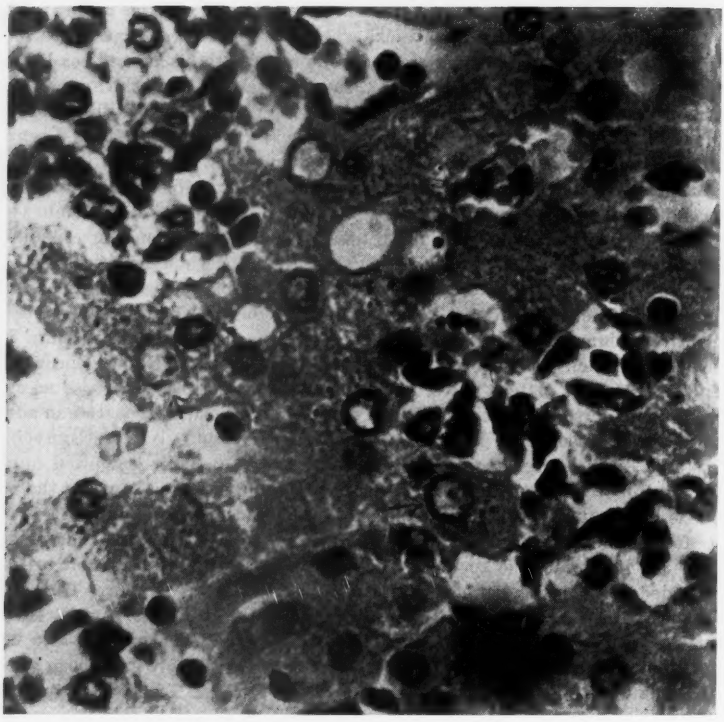

Fig. 1. Liver preparation with probable inclusion bodies.

round, cellular elements, uniform in size, with sparse cytoplasm and nuclei comparatively large as compared with the cell volume. These nuclei are somewhat larger and less chromatic than those of mature lymphocytes, and rather closely resemble the nuclei of the cells usually present in germ centres. The cellular elements described are immature, and most probably they are to be regarded as reticulum cells. Further, in several fields there are larger cells of the reticulum cell type, either single or collected in small groups, and lastly, here and there within the tissue leukocytes with eosinophilic granules are noted. There is no evidence of necrosis, and neither giant cells nor lipophages are observed. The *salivary gland tissue*, is crammed with round cells similar in appearance to those mentioned in the foregoing.

In the *spleen* only sparse, rather small lymph follicles containing germ centres are noted. The red pulp is hyperaemic and markedly cellular. The cells present are rather monomorphic and for the most part consist of immature cell elements suggesting reticulum cells, with round, not particularly chromatic nuclei. In addition there are eosinophil leukocytes as well as some larger, immature, frankly pathological cells. In the spleen as well as the lymph node, the argyrophil reticulum meshwork shows a very high degree of development and partly ramifies into delicate filaments curling

between the separate cell elements. The development of the reticulum is most marked in the lymph node.

In the *liver* very large cell infiltrations, rather suggestive of neoplasia, are observed principally in the periportal connective tissue and adjacent portions of the hepatic parenchyma, but also, in smaller aggregations, between the liver cell columns. These infiltrations are composed of very immature cells, which partly resemble reticulum cells; their actual character defies identification. Apart from these cells, which predominate among those present, there are small lymphocytes and a fair proportion of leukocytes with eosinophil granules. Within some of the liver cell nuclei the chromatin is collected in a capsule-like membrane occupying the peripheral zone of the nucleus. In these nuclei there are sparse, small, quite indistinct, amorphous bodies which, so far as can be ascertained are acidophilous. They are somewhat suggestive of inclusion bodies.

The *kidneys* contain extensive infiltrations similar in type to those found in the liver. The *adrenals* do not present pathologic alterations.

Hence, the histological picture of the material examined discloses a very pronounced reaction involving principally the reticulo-endothelial system. Certain histological details seem to suggest that the alterations observed might be due to a virus infection. Patho-anatomical diagnosis, reticulosis (Dr. C. Lundmark).

Discussion

The fatal course of disease, the haematological changes, the splenomegaly, the pyrexial attacks, and the elevated sedimentation rate actually suggest Letterer-Siwe's disease. The periodic blood eosinophilia and the presence of eosinophil leukocytes in the tissues examined histologically would seem to point to eosinophilic granulomatosis. According to BRAIN, reticulosis may give rise to focal involvement of the pachymeninx and spinal cord, which would explain the baffling impediment in walking that introduced the disease. The general improvement in the patient's condition, which commenced towards the end of May, 1951, i.e. roughly five months after the onset of the disease, is rather hard to explain. The only possibility of this resulting from the treatment is, that aureomycin, which was given provisionally at intervals, might have acted upon a possibly infective process. In his report the pathologist who examined the microscopic sections, suggests that certain details might be considered to indicate a virus infection, which would seem to support this hypothesis.

Summary

In a boy, age two years, an impediment in walking was noted. By degrees marked anaemia with splenic enlargement, thrombocytopenia, elevation of the sedimentation rate, and bone marrow findings pointing to reticulosis or leukaemia. All the symptoms subsided, and the patient was fairly comfortable. He was fairly well for about one month. Subsequently his condition deteriorated once more, and he died roughly seven months after the onset of the disease. Pathoanatomic diagnosis, reticulosis.

Un cas de réticulo-endothéliose d'évolution inhabituelle.

Chez un garçon de deux ans, on remarque une faiblesse à la marche. Progressivement apparaissent une anémie marquée avec une augmentation du volume de la rate, une thrombocytopénie, une élévation du taux de sédimentation et des résultats de

moelle osseuse indiquant une réticulose ou une leucémie. Tous les symptômes régressent et le malade était pratiquement en bon état. Il fut tout à fait bien pendant environ un mois. Par la suite, son état est devenu plus grave qu'autrefois et il est mort environ sept mois après le début de la maladie. A l'examen anatomo-pathologique: réticulose.

Ein Fall von Retikuloendotheliose mit ungewöhnlichem Verlauf.

Bei einem Jungen wurde im Alter von 2 Jahren eine Behinderung im Gehen festgestellt. Nacheinander kamen deutliche Anämie mit Milzvergrösserung, Thrombocytopenie, Erhöhung der Blutkörperchensenkungsgeschwindigkeit und Knochenmarkbefunde wie bei Retikulosen oder Leukämien hinzu. Alle Symptome verschwanden und der Patient war praktisch beschwerdefrei. Das gute Befinden dauerte etwa einen Monat. Anschliessend verschlechterte sich sein Zustand wieder, und er starb 7 Monate nach Auftreten der Krankheit. Pathologisch-anatomische Diagnose: Retikulose.

Caso de reticuloendoteliosis con evolución poco corriente.

En un niño de 2 años de edad apareció impedimento a la marcha. Progresivamente aparecieron severa anemia con esplenomegalia, trombocitopenia, aumento de la velocidad de sedimentación y alteraciones de la médula ósea del tipo de una reticulosis o leucemia. Todos los síntomas remitieron encontrándose bien durante un mes, aunque luego la enfermedad evolucionó rápidamente muriendo al cabo de 7 meses después del comienzo de la enfermedad. Diagnóstico anatomopatológico: reticulosis.

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Department of Paediatrics
Lasarettet
Norrköping. Sweden

Use of Hyaluronidase in Scleroderma

by ULLA CLAESSON and BERTIL LINDQUIST

From the Pediatric Clinic, University of Lund, Sweden. Chief: Professor Sture Siwe, M. D.

Scleroderma is a disease that may manifest itself in several ways. Most often it is to be found as a localized form in the skin, which is thickened and adherent to the underlying tissue. The epidermis is waxy and more or less atrophic. This type of scleroderma, generally called morphoea, is a relatively harmless condition with good prognosis. Another type of this disease is the generalized progressive form, which is a very serious disorder. The skin changes are principally the same as those described above, but larger areas of the body are affected, and the subcutaneous tissue and the underlying

muscles are involved. Visceral lesions are sometimes present. Although oesophagus is the organ most often affected, changes have also been observed in other parts of the digestive tract, and in the heart and the lungs (O'Leary and Waisman, Weiss *et al.*). The onset of the disease comes usually slowly with a continuous progress of the changes and consequently bad prognosis. According to Conn no generally accepted and effective treatment, either causal or symptomatic is at present known.

In the following a case of scleroderma interpreted as a generalized form will be described. It may be of interest as we have noted a good effect by treatment with hyaluronidase, a preparation not earlier tried in this condition.

Case report

A 10 year old girl was admitted to the clinic on the 16th June 1951. In the beginning of May 1951 a white plaque was observed on the inside of her right forearm. One month later the girl was unable to stretch out her arm properly.

Physical examination revealed nothing noticeable beside skin lesions in her right arm. The general health of the girl was good. In the regio deltoideus there were some irregular stripes of shiny atrophic skin. Further she had a few plaques — the largest about 3 × 5 cm — of similar appearance involving the lower half of the inside of the forearm. These lesions were adherent to the underlying tissues. Musculus deltoideus was moderately atrophic. The musculature of brachioradialis was indurated and the same was the case with the muscles belonging to digiti I and II. The skin over these changes was initially intact. There was a defect of about 70° in the extention of the elbow. Further the patient was unable to clench her hand and to opponent digiti I and V. The flexion of the hand was limited to about 15°.

Laboratory findings included normal values for haemoglobin and blood corpuscles. Calcium, phosphorus and alkaline phosphatases in serum were normal. Roentgenography of the entire digestive tract, cor et pulm, cranium, columna and joints revealed nothing pathological. On the electrocardiogram the S-T interval was elevated in the second lead. Electroencephalography and electromyography were normal. 17-ketosteroids in the urine were within normal limits. Glucose tolerance test showed nothing pathological. The microscopic examination of the skin revealed an increase of the collagenous tissue and a decrease of the elastic fibres in the corium. There were perivascular infiltrations of lymphocytes and plasma cells. Biopsy of the brachioradialis showed similar perivascular infiltrations and an increase of the collagenous tissue.

Course and treatment. The patient was given hyaluronidase (Hyalas Leo) 10 V.R.U. twice daily in intramuscular injections. A remarkable improvement with regard to the motility of the elbow joints was noted within one weak; the defect in the extension decreased to about 30°. The condition then appeared to be stationary and the hyaluronidase therapy was discontinued after 3 weeks. On account of favorable results described in literature by treatment with ACTH (see below), the patient was given 10 mg twice daily of this preparation. Adequate response was noted in the eosinophilic count. But during this period — 15 days — there was a marked progress of the disease. The previous skin lesions extended and new cutaneous plaques appeared along the musculus brachioradialis. There was also a certain progress in the muscle contractures. The medication was then changed to para-amino-benzoic acid, given in a dosage of 12 g daily during 3 weeks. In this period the symptoms also progressed, but more slowly. Then hyaluronidase was administered again and the patient has got

this medication continuously for the last ten months. No symptoms of intolerance have been noted. During this second period of treatment with hyaluronidase the progress of the disease was initially arrested, and thereafter a slow but constant improvement of the condition was registrated. The skin lesions were not so tense and the tissue induration has shown a considerable regression. The general health of the patient is at present still good, i.e. one year after the onset of the disease.

Discussion

As mentioned above regarding the therapy of scleroderma no remedy has been reported that can claime to get at the essential cause of the disease. Generalized scleroderma is to be regarded as a diffuse fibrous disease with a general collagene degeneration, especially of the skin and muscles. According to this we have regarded it justified to try hyaluronidase in this condition. It is apparent that there has been a good effect of this agent in the case described above. The beneficial effect of hyaluronidase is more striking in comparison with the other therapeutics used, which in this case had none or contrary effect. The closer mechanism for the mode of action of hyaluronidase in the treatment of scleroderma will not be dealt with in this connection, because at present one lacks accurate knowledge of the action system of hyaluronic acid, hyaluronidase and hyaluronidase inhibitors in the tissues. An extensive discussion would therefore be too speculative to be of any value.

Considering treatment with ACTH there are different results reported in the literature. GUSMAN and RUDOLPH for example, noted complete remission of the lesions, while BRODTHAGEN, REYMANN and SCHARTZ, registrated no beneficial effect. From experimental point of view (SEIFTER, BAEDER and DERVINIS, EKMAN, THUNE and TRUEDSON) results have been reported about an inhibiting effect of cortisone on the hyaluronidase action. With regard to the treatment with para-amino-benzoic acid ZARAFONETIS, CURTIS and GULICK have tried this agent in six cases of scleroderma and dermatomyositis. In two cases they obtained an excellent effect, in three cases a certain improvement and in one case no effect at all. Further several other therapeutics inter al. vitamin D and E have been used in the treatment of scleroderma but without great success.

The beneficial effect of hyaluronidase in the case reported above must be taken with a certain reservation especially with respect to the occurrence of spontaneous remissions. The long observation period after the onset of the hyaluronidase treatment together with the usual course of disease argues, however, against such an interpretation.

Summary

One case of generalized progressive scleroderma in a 10 year old girl is described. ACTH and para-amino-benzoic acid had no or contrary effect, while hyaluronidase showed a good effect on the skin lesions as well as on the tissue indurations.

Emploi de la hyaluronidase dans la sclérodérmie.

Un cas de sclérodermie généralisée progressive chez une fillette de 10 ans : L'ACTH et l'acide para-aminobenzoique ne donnèrent ou aucun effet ou une aggravation tandis que lá hyaluronidase produisit un bon résultat sur les lésions cutanées aussi bien que sur les indurations des tissus.

Verwendung von Hyaluronidase bei Sclerodermie.

Ein Fall von generalisierter progressiver Sclerodermie bei einem 10 Jahre alten Mädchen wird beschrieben. ACTH und Para-amino-Benzoesäure hatten keinen oder einen ungünstigen Effekt, während Hyaluronidase sowohl auf die Hautläsionen als auch die Gewebsverhärtungen einen guten Einfluss erkennen liess.

Empleo de la hyaluronidase en el esclerederma.

Se describe un caso de esclerederma generalizado progresivo en una niña de 10 años. El empleo de ACTH y ácido paraamino benzoico no mostró ningún efecto, mientras que el empleo de hyaluronidasa mostró un efecto favorable tanto sobre las lesiones cutáneas como sobre los tejidos indurados.

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Barnsjukhuset
Lund. Sweden.

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PROCEEDINGS

Proceedings of the Pediatric Society of South Sweden

Meeting at Malmö, November 30, 1952.

S.-I. Björklund: Congenital adrenal dysfunction.

An 11 day old boy with shock, cyanosis, vomiting, and sanguineous, mucous diarrhoea. Breast milk and parenteral supply of fluids did not produce any noticeable improvement. When he was 25 days old an arrhythmia cordis was discovered and there were ECG changes as in hyperpotassemia. DOCA and continued infusion of sodium chloride elicited an improvement. The urinary 17-ketosteroid excretion ranged 2 to 5 mg per 24 hours. At 1 year of age the penis began to enlarge and pubic hair developed. The 17-ketosteroids rose to 11 mg per 24 hours (Hamburger) and the excretion of 11-oxysteroids was 0.8 mg per 24 hours (Sprechler). At 17 months of age cortisone therapy was instituted first with 50 mg, later 35 mg per 24 hours intramuscularly for 10 days followed by 25—37.5 mg per os pro die. The 17-ketosteroids fell to 3.3 mg per 24 hours and the 11-oxysteroids to 0.3 mg per 24 hours. No extra sodium chloride was supplied during this period. There were no symptoms of addisonism. After 3 months therapy the penis was of normal size but the growth of the pubic hair had not diminished. At 18 months of age the 17-ketosteroids are around 3—7 mg per 24 hours. The ACTH-test with 10 mg gives a significant drop in the eosinophils. This is thus a case of congenital dysfunction of the adrenal cortex with insufficiency of the so-called electrolyte-regulating hormone and increased secretion of the glucocorticoid and androgen fractions. Cortisone therapy has depressed the latter two, while it has not affected the former unfavorably.

S. Axtrup: Intravenous nutrition of premature infants with low body weights.

It has been widely emphasized that in order to reduce the risk of aspiration in premature infants of low body weight the peroral supply of food should be postponed for several days and the fluid loss replaced by subcutaneous infusions. The author has instead experimented with intravenous administration of nourishment and liquids. A polyethylene tube was introduced into the saphenous vein at the malleolus when the infant was a day or two old. In the tube were injected repeatedly small doses of Ringer's solution, glucose solution, plasma and blood. Oxygenated fresh blood was administered daily in small quantities to furnish extra oxygen as well as respiratory enzymes and also to provide fresh antibodies. Blood has in addition, of course, a nutritional value. The advantage of this method of treatment is that the peroral supply can be postponed until it presents no difficulties. In one of the author's cases it had to be postponed for 8 days. Even peroral feeding is carried out most easily by means of a polyethylene tube which via the nose is brought down into the stomach and allowed to remain there. — The mortality in the lowest weight classes is high. In a series of cases from Gothenburg it was 98 % in the group weighing less

than 1 kg and 61 % in the group between 1 and 1.5 kg. Attempts must be made to reduce this mortality. With the method outlined here two infants with birth weights of 950 g survived. This encourages us to continue with this practice.

P. Selander and *A. Syrrist:* **The pacifier, its frequency and influence on the milk teeth.**

Of 1332 children ranging in age from 10 months to 5 years from the Child Welfare Center in Malmö 34.2 % had used pacifiers. Sugar pacifiers had been used by 6.3 % This practice was most common in social group III (39.1 and 8.4 % respectively). When a pacifier was employed it was usually when the child was from 1 to 4 months of age. At 3 to 5 years of age those who had used an ordinary pacifier exhibited a poorer dental condition than children who had not. In this age group those who had been given sugar pacifiers, even after they were 10 months old, had the poorest dental condition. Children with a good dental condition in the ages 10 months to 2 years had employed sugar pacifiers, even after 10 months of age, considerably less frequently than those with an exceptionally poor dental condition. The caries-producing effect of pacifiers seems to be evident from the somewhat higher frequency of totally decayed maxillary incisors in children who have used pacifiers than in those who have not. The practice of sugar pacifiers is attended by a characteristic picture of caries, with the first and heaviest attack towards the gums on the labial surfaces of the maxillary incisors. If the child has employed a sugar pacifier during dentition the teeth are attacked from the incisal edge and are destroyed gradually as they appear.

P. Selander and *H. Grahnén:* **Rickets, spasmophilia and changes in the permanent occlusion.**

Three groups of young people were examined at the College of Dentistry in Malmö, all of whom had been admitted to Flensburg Children's Hospital as infants. Group I had been hospitalized for rickets, group II for spasmophilia, while the cases in group III showed no signs of rickets or spasmophilia at the usual clinical examination. The investigation was aimed primarily at the occurrence of hypoplasia of the enamel, caries, crowded or abnormal positions of the teeth, possible defects in the jaws (from roentgenograms and impressions). It was possible to record only the macroscopically visible defects. The average age at which the follow-up-examination was performed was for group I 17.4 years, group II 18.7 years and group III 15.6 years. The series of rachitic cases exhibited symmetric hypoplasia of the enamel in 27.4 %, in the series of spasmophilic cases the corresponding figure was 73.2 % and in the control series 3.1 %. Statistically significant differences are obtained. Hypoplasia of the enamel was encountered in both mild and severe forms of rickets and spasmophilia. No certain difference in type, localization and degree of severity of the defects could be demonstrated between the rachitic and spasmophilic series. There was no variation in the frequency of caries in the 3 groups. No sexual difference in the occurrence of hypoplasia and caries could be shown.

G. Björkman and *L. Sonesson:* **Endocardial fibro-elastosis.**

The etiology of hyperplasia of the endocardium is not clear, but most likely it is caused by a developmental anomaly. The main feature of the morbid picture is a failing of the left side of the heart. As a rule there is a considerable enlargement of

this part and uncharacteristic murmurs on auscultation. The ECG is often normal. Pathologico-anatomical diagnosis:— thickened endocardium in the left half of the heart, occasionally also involving the right side. The mitral and aortic valves can be involved. Microscopy reveals fibro-elastic tissue elements but no evidence of inflammation. The prognosis is poor; mild cases can be asymptomatic for several years. In all cases of idiopathic cardiac enlargement and sudden death in infancy this disease should be borne in mind. Two cases of this disease, both boys, have been treated at Flensburg Children's Hospital. One died at 2 days of age and the other at 3 months. Autopsy revealed changes typical of endocardial fibro-elastosis. In a third case, a 2 year old boy, the probable diagnosis of endocardial fibro-elastosis was based on the clinical picture which showed, among other features, cardiac enlargement and mitral insufficiency on angiocardiography.

P. Selander: 490 cases of pseudocroup; statistics and therapy.

Since August 1949 there has been a marked increase in the number of cases of pseudocroup, which prior to this time ranged from 15 to 50 cases every year in the hospitals in Malmö. The affection has been most common in the winter and most unusual in the middle of the summer. The seasonal curve coincides with those of diphtheria, scarlet fever and epidemic hepatitis. As to the age distribution pseudocroup is most like diphtheritic croup and scarlatina. Pseudocroup occurs, however, in no less than 97 % of the cases in children under 7 years of age and has an obvious peak at the age of 1 or 2 years. The other two are not so markedly diseases of early childhood. A good 65 % of the cases were boys, which is unique for an epidemic disease. The same sex distribution is found in the cases of asthmatic bronchitis, eczema, rickets and spasmophilia admitted to Flensburg Children's Hospital. During the epidemic the mortality and frequency of tracheotomies decreased, generally speaking, the frequency of severe cases. Only a certain percentage showed Haemophilus influenzae in the throat tests; severe cases were more common in this group. A little more than one fourth of the cases were afebrile the whole time. A little more than one third were febrile for 3 days or more. A double-peaked fever curve was obtained in 16 % of the febrile cases. Almost one half of the cases had a blood sedimentation rate of less than 15 mm in one hour, while one fourth had sedimentation rates over 25. All tracheotomized children had a high sedimentation rate when admitted to the hospital. The frequency of tracheotomy was 1.6 % and the mortality 0.8 %. Of the last 180 children the odd cases were given sulphonamides and penicillin and the even cases chloromycetin. The treatment was otherwise the same. The nursing period was equally long in both groups, but it appears as though the group receiving chloromycetin had one more febrile day. No death occurred in either group. (This investigation is being continued.)

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BOOK REVIEWS

J. O. Polleri: **El Prematuro.**

Editorial Garcia Morales, Montevideo. 1952, 273 pp.

The author, who is head of the Casa del Nino in Montevideo, has devoted himself to the study of premature infants. This volume is a report of his experiences of 4,000 infants. The frequency of premature birth in Montevideo is 5—15 % according to various statistics. In special chapters the mortality, neonatal disorders, feeding and care of the infants and the pathogenesis and prevention of premature birth are discussed. Polleri uses roughly the same principles as in Scandinavia and his experiences correspond fairly well to our own. He takes due consideration of the Anglo-American and Scandinavian recorded experiences. In order to prevent pulmonary infection and atelectasis Polleri recommends keeping the infants in the erect position for some hours twice a day to facilitate breathing. The pathogenesis and prophylaxis of rickets and anemia are covered. Retrolental fibroplasia does not exist in Uruguay. The book gives an excellent review of our present knowledge in the field of prematurity written by a well-experienced and sympathetic Uruguayan collegue.

L. F. Meyer and *E. Nassau:* **Physiologie und Pathologie der Säuglingsernährung.**

S. Karger, Basel, 1952. 474 pp. Price SFr. 52.

The authors, who had their training at the clinic of Finkelstein in Berlin and occupied important pediatric positions in the pre-nazistic Germany, are now at the head of the preventive pediatrics movement in Israel. When they left Germany the infant mortality rate in that country had declined considerably. In the new Israel with its high infant mortality rate they had to make a new start in the campaign to promote an improved child health among the Jewish immigrants. In their book they report their new practical experiences in the light of the present-day knowledge of nutritional disorders and their prevention and treatment. The book does not contain many new data for the specialist but is rather to be regarded as an excellent compilation of our present knowledge in puericulture for students and general practitioners. It is, however, of interest also for the child specialist to read of the experiences of these two well-known pediatricians from their new home-country, Israel.

A. M. de San Martin: **Alimentacion del lactante. Technica y educacion alimentarias. Profilaxis de los estados carenciales.**

Editorial Artecnica, Buenos Aires, 1952. Price Pesos 20.

The author of this nice little book is Associate Professor of Pediatrics at the Faculty of Medicine of Buenos Aires. It contains an outline of the principles of natural and artificial infant feeding for students and educated mothers. The opinions expressed and the methods recommended correspond fairly well to those prevalent in Western Europe and are based to a great deal on the old German school. The matter is presented in an interesting way and the book can be recommended to those who want to know the methods and the teaching of puericulture in Argentine to-day.

Martin Bodian: **Fibrocystic Disease of the Pancreas.**
W. Heinemann, London, 1953. Price 63 s. 244 pp.

The well known pathologist at the Hospital for Sick Children, Great Ormond Street in London, Martin Bodian in collaboration with the clinician A. P. Norman and the genetist C. O. Carter, has collected the data regarding the 116 cases of fibrocystic disease of the pancreas that have been treated at the hospital in 1943—1950. Dr. Bodian gives a short historical background to the development of our present conception of the disease as a genetically determined general disorder of the secretion of mucus. The comparison made regarding the signs and symptoms of fibrocystic disease of the pancreas with other kinds of pancreatic disorders leading to a deficient excretion of enzymes is very illuminating as to the "mucoviscidosis" theory of the former disease. The clinical observations and especially the patho-histological studies are presented in an excellent way and although these experiences do not bring out any fundamentally new facts they nevertheless constitute a very interesting and valuable confirmation of the results of researches in other quarters. Those who have had the privilege to visit the Hospital for Sick Children and be acquainted with the admirable manner of registration of case records used in Dr. Bodian's department expect nice photos, figures and tables illustrating the text of the book, and this expectation will be greatly filled. The book can be warmly recommended both to the clinician and the pathologist.

Hans Selye **and** ***Alexander Horava:*** **Second Annual Report on Stress.**
Acta, Inc. Medical Publishers, Montreal, 1952. Pp. 526.

Reference to 4 000 publications that have appeared in 1951. The classification of the references facilitates the reader to find the latest facts on stress for which he is looking. In a note the authors request that reprints of articles which deal with problems relating to research on stress and the s.c. adaptive hormones (ACTH, STH, corticoids, adrenergic substances etc.) should be sent to them as soon as they are available (address: Case Postale 6128, Montreal).

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NEWS AND COMMENTS

Die 53. Tagung der *Deutschen Gesellschaft für Kinderheilkunde* findet vom 10.–13. September d. Js. in Bad Kissingen unter dem Vorsitz von Professor Dr. de Rudder, Frankfurt/Main statt. Als Hauptvorträge sind vorgesehen

1. Nicht-rheumatische Knochen- und Gelenkerkrankungen,
2. Haematologie (Erythropoese — Gerinnung — Leucaemie),
3. Krämpfe im Kindesalter.

Vortragsanmeldungen (Auswahl begrenzt) mit genauer Inhaltsangabe werden bis zum 15. Mai 1953 an den Vorsitzenden (Frankfurt/Main Universitäts-Kinderklinik, Ludwig Rehnstr. 14) erbeten. Mit der Tagung ist eine *Wissenschaftliche Ausstellung* verbunden.